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Review article

Viruses: As mediators in "*Élan vital*" of the "creative" evolution

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ABSTRACT

The understanding of the processes occurring in Nature has been a continuing concern throughout the history of mankind. Intellectual tools employed towards this goal were specific for each period and have been largely based on the prevailing paradigms that reigned in the past. In this work we present evidence that supports the idea of viruses as key agents mediating natural processes linked to the evolution of organisms, particularly those involved in the flux of genes in the environment. This point of view tinges our perception of Nature and prompts us to include "viral" creativity and plasticity among the tools we employ to analyze those processes far beyond actual paradigms. Experimental data to support this proposal arose during the study of the interaction of the human pathogen, herpes simplex virus (HSV) with sulfated polysaccharides during multiplication of the virus in vitro. Sulfated polysaccharides are the main chemical structures found in carrageenans (CGNs) that are natural products obtained from seaweeds, which proved to be strong inhibitors for the virus. Here we describe the interaction between virus and CGNs as a suitable scenario for the emergence of viral variants which proved to be markedly attenuated for mice. A striking feature of these variants is that they showed changes at the level of conserved regions of the genome such as the DNA polymerase and thymidine kinase genes. In view of these findings, the importance of HSV evolution towards attenuated variants by the action of polysaccharides is also discussed. Attenuation may be considered part of a natural evolutionary process enabling the virus to contribute with valuable information for the host.

Contents

1. Introduction

Living organisms may develop new capabilities by acquiring genetic information from the surrounding environment, in the form of "content-loaded signs", relevant for their survival, signaling and communication (Witzany, 2006). These "content-loaded signs" can be used at different levels of organization and complexity, starting with single molecules up to complex ecosystems. Moreover, to decode the context-dependent content of these signs, biological agents must be capable of their correct interpretation, that is, the so-called context involvement. At the level of a single cell, the complexity of the "content-loaded signs" and their interpreter networks is already immense. Living systems are composed of interacting networks of autonomous agents,

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all capable of sensing signs, interpreting their content according to their context and acting on their own behalf (Kauffman, 2000, 2007; Kauffman and Clayton, 2006). These interacting networks may be interpreted as a complex text and the genetic code as a language (Witzany, 2011a). As argued by Witzany the origin and the continuous editing of this language would require the participation of ubiquitous agents, competent in language (Witzany, 2006, 2011b). On this line, viruses which are able to colonize every cell of an organism in a persistent, non-lytic way are proposed to be these ubiquitous agents. In most cases, they are not widely functional ("defectives") and serve as species-specific (and most often tissue-specific) co-opted adaptations, i.e. regulatory elements that are part of an integrated network of gene regulation (Villarreal, 2005). Within this virus-first perspective, viruses are the most abundant genetic sequences on this planet, and cellular genomes, their natural habitat, are a limited resource for this abundance. From this point, the viruses are the essential agents of life. On this line, Villarreal coined the concept of "genetic addiction modules". An apparent sense of belonging is essential to all forms of life, from bacteria to humans. This sense is crucial in determining the complex intra and interspecific relationships among members of the same species and members of other species, respectively. This is a basic cooperative nature of life that Villarreal calls "group membership" (Villarreal, 2009a). However, cooperation among living organisms is not easily accounted for by the current theory of evolution, yet even viruses display group membership. Viruses clearly affect bacterial group membership, which are the most diverse and abundant cellular life form on Earth. Viruses are the most ancient, numerous and adaptable biological entities we know. Viruses not only can cause acute disease, but also persist as stable "unseen" agents in their hosts, attaining stability in evolution. It is from such a persisting relationship that viruses can inform us regarding the strategies and mechanisms of "group membership". In order to persist in their hosts, viruses must be able to resist other viral competitors and at the same time, be "unseen" by the immune system of the host. During persistent infection, viruses were the first genetic elements to show a strategy called an addiction module. In addition, persistence often involves mixtures of viruses that can even include non-viable, defective, even "dead" members which work cooperatively to attain fitness. With these characteristics, viruses can introduce into their host new genetic identities that create group identities and group immunity, including altruistic-like individual self-destruction used for the protection of the group. Addiction modules can compel cooperation and symbiosis between individuals. From this perspective of genetic parasites and addiction modules, we can identify events leading to the evolution of group identity (immunity) and group cooperation in all life (Villarreal, 2008).

On this line, the term "*Élan vital*" (literally, vital impetus), introduced by French philosopher Henri Bergson (1859–1941) in his famous work "*L'évolution créatrice*" (1907), represents a suitable scenario for viruses to carry on with this task. Life, Bergson says, is not reduced to mere physical or chemical phenomena, nor is it directed teleologically, but an impulse that has a certain orientation. Then, "*Élan vital*" may be understood as a "stream (or impulse) that goes from one living organism to another" generating variability and being the real cause of evolution in Nature (Bergson, 1998).

2. Viruses as essential agents of life

Massive viral colonization occurred from the very beginning of cellular life, starting with the evolution of Bacteria and Archaea and, as recently suggested, Eukarya in parallel (Boyer et al., 2011; Forterre, 2011). In this sense, the formation of all kingdoms, their families, genera and species was based on the consequences of several viral infection events and resulted finally in the appearance of diversified lineages and ultimately in the evolution of new species (Villarreal, 2005).

Today, viruses are recognized as the most abundant form of life in the oceans (Bergh et al., 1989). It is estimated that 10^{30} viruses live in the ocean and 10^{23} viral infection events occur per second. They are the major source of mortality for all living organisms in the sea but, also major settlers in their genomes that serve as immune functions against infections by closely related viruses (Suttle, 2007; Villarreal, 2011). The passage from sea to land of primitive organisms also brought viruses that faced the problem of infection in a non-aqueous medium. This problem was solved, at least in part, by dispersion through fomites or infection by direct contact between organisms sharing corporal fluids. In this line, persistent infection of organisms by viruses tends to solve this problem by modulating immune system of the host in order to impair the immune response that otherwise would be able to combat the infection leaving thus the virus free to infect new hosts. Interestingly, persistent DNA viruses within mammalian genomes have been recently reported (Horie and Tomonaga, 2011). Viral persistent infections accompany the host during its entire life, usually as unapparent infections. To achieve persistence, viruses need to modulate cellular processes, those particularly involved in response to stress and apoptosis to impede the infected cell to die. Also, it is important to take into account that these strategies must be able to operate, as stated above, superimposed on the innate and adaptive immune responses of the host (Vilarreal, 2007). Transposable elements in cellular genomes are the most likely remnants of viral unapparent infection events (Goodier and Kazazian, 2008, O'Donnell and Burns, 2010). In addition, the repeat sequences of mobile genetic such as LINEs, SINEs, LTR-retroposons, non LTR-retroposons and ALUs are clearly related to retroviruses, as are reverse transcriptases (Batzer and Deininger, 2002; Eickbush, 2002). Also, repeat sequences found in telomeres and centromeres are most likely to be of viral origin (Witzany, 2008). There are strong indicators that these structures are derived from retroviral infection events and currently act as modular tools for cellular needs (Weber, 2006). During infections, whether acute or persistent, increasing levels of complexity and diversity occur through variation, i.e., inheritable genetic innovation, new combinatorial patterns of genetic content and a variety of non-coding RNAs that serve as regulatory networks and modify the genomic content (Domingo, 2011; Witzany, 2009a).

In this sense, it may be speculated that the world would be much more viral and diverse than once we thought. And viruses along with their regulators seem able to do practically everything needed for life, from promoting photosynthesis (Lindell et al., 2004), providing core genes for translation (Abergel et al., 2007), encoding cytochrome p450 (Lamb et al., 2009), transferring entire metabolic pathways (Monier et al., 2009), to providing most protein folds (Abroi and Gough, 2011), controlling placenta specific genes (Lynch et al., 2011), controlling most aspects of innate and adaptive immunity networks (Hengel et al., 2005; Miller-Kittrell and Sparer, 2009) or controlling expression of primate P53 (Wang et al., 2007). Indeed, in a meta-analysis of metagenomic data of over ten million protein encoding sequences, it is the products of virus (such as transposases or capsides) that are the most prevalent genes in nature (Aziz et al., 2010). The implications of the massive omnipresence of viruses can no longer be ignored in the arena of evolution.

Even though DNA viruses may represents tools by which the cell acquires new features, it cannot be ignored that RNA viruses may play an important role too. The main role of DNA is relativized through the detection of the early RNA world and its abundance of RNA agents and ribozymes that cooperated and competed in consort. The RNA-agents play important roles in all regulatory processes of translation, transcription, recombination, epigenetics and repair, as well as its regulation of all the developmental processes of cellular life. In some organisms, such as humans, non-coding RNAs represent the most abundant part of the genome (Witzany, 2009b).

On the other side, it became increasingly clear that cellular DNA is not a fixed structure, but is dynamically constituted. In parallel, it also became increasingly clear that there are many regulatory elements, vital for expression patterns and silencing of genes. The discovery of epigenetic marking opened the perspective of the whole genome being

marked for transcription and translation, and that these markings can change according to the surrounding conditions or stress-related experiences. In this line, viruses may act as epigenetic markings regulating the DNA genome of the host.

Another interesting point to address concerning viral biology is the fact that virus populations exist as quasispecies (QS). Virologists currently use the term QS to refer to distributions of non-identical but related genomes that are subjected to a continuous process of genetic variation (cooperative, competitive, defective and even lethal types); in this concept, the "clouds" of genomes, rather than individual genomes, function as units of selection (Martinez et al., 2012; Ojosnegros et al., 2011). Due to their high mutation rates, rapid generation time, and short genomes, RNA viruses are an excellent and simple tool for using experimental virology to explore and challenge population genetics and system biology concepts, including QS concept, fitness variations (Holland et al., 1991), Muller's ratchet theory (Chao, 1990), the Red Queen hypothesis (Clarke et al., 1994), etc. Evidence shows that single-stranded DNA viruses (all with genomes smaller than 13 kb) evolve at rates approaching those observed in their RNA counterparts (Duffy et al., 2008). However, little information is available for large DNA virus, although it seems clear that they evolve more slowly than RNA virus (Drake and Holland, 1999). Despite this feature, large DNA viruses are genetically creative and not simply thieves that take genes from host genomes. By far the most productive sources of viral genes are those large DNA viruses that infect prokaryotes and unicellular eukaryotes. In these cases, novel viral genes appear as a consequence of recombination between viruses. Novel viral genes would constitute the basis for genetic material to be transferred to eukaryotic genomes (Villarreal, 2009b) and settles the mechanisms by which virus and host cooperate for evolution (Domingo et al., 2012.). In this sense, several years numerous proposals have been published that suggest viruses may symbiotically contribute to host evolution, including several hypothesis suggesting that DNA viruses and retroviruses might be involved in the origin of the DNA replication apparatus for all three domains of life (Forterre, 2006a, 2006b; Koonin et al., 2006; Vilarreal, 2007).

Considerations exposed above account for the possibility that "*Élan vital*" relies on viruses to operate in Nature. The agent-based perspective is evident in the observation that every coordination process between cells, tissues, organs and organisms depends on signs that function as signals between signaling agents. Signaling and communication does not occur by signals alone, but by living agents that are competent to use signs, i.e. organisms and viruses. In all cases, the participating agents share a competence to generate signs, to receive appropriate messages and to interpret their contents. Virus is one the ways by which genetic information have adapted to survive in this biosphere (Witzany, 2012).

3. Relationships between the cell wall of red algae, carrageenans and viruses

The cell wall exerts considerable biological control over individual cells and organisms, thus playing a key role in their interactions with the environment. Significant progress has been made over the past 40 years in our understanding of the structure, synthesis, and function of plant cell walls. Recently, and potentially driven by the awareness that "small modifications in their chemistry can have profound effects on the multifarious functions cell walls perform" (Niklas, 2004), new studies towards the understanding of plant cell-wall evolution have been settled based on investigations about the origins of cell walls. Niklas highlighted that cell walls have deep roots in the tree of life (Niklas, 2004). One important feature to take into account is the fact that sulfated polysaccharides are key constituents of cell walls of marine algae. Sulfated wall polysaccharides from marine plants and algae may confer an adaptative advantage through possible structural and osmotic functions that are correlated with an environmental pressure. Also, cell walls participate as a first defense against the attack of to the pathogens. On this respect, cell-wall fragments can elicit signals leading to a defense response (Cosse et al., 2007). In many cases, this response associated to an oxidative burst and mediated by the production of hydrogen peroxide may be considered a primitive immunity of algae (Bouarab et al., 1999; Correa et al., 1988), as well as secondary metabolism or release of free fatty acids which are subjected to an oxidative cascade involving lipoxygenases, cyclooxygenase-like and cytochromes P450 enzymes (Bouarab et al., 2004). The presence of these animal-related genes and some traits of metabolism implied as a consequence are in concordance with study of Nozaki et al. (2003), which puts red algae as the most basal eukaryotic photosynthetic group (Nozaki et al., 2003).

Galactans present in the cell wall of red algae are named carrageenans (CGNs). CGNs have similar structures to the molecular pattern observed for glycosaminoglycans (GAGs). GAGs are found mainly in the cell surface as heparan sulfate (HS). CGNs are also known for their wide and variable physicochemical properties which make them suitable for different applications in the fields of food, medicine and pharmacology. They have proved to be useful tools due to their immune-modulator and antitumoral activity, their interference in the clotting system and in the inflammatory processes and moreover by affecting viral replication (Carlucci et al., 1999a, 1999b, 2012; Pujol et al., 2007; Yermak et al., 2003). For most of the viruses affected by CGNs, the initial bond of the virus to cells is mediated by the interaction of a viral protein located on the surface of virions with a molecule of GAG in the cellular surface in the form of HS (Esko and Selleck, 2002).

The eukaryotic algae are among the oldest eukaryotic microorganisms for which there exist clear geological data (Knoll, 1992) and all classes of algae have their specific DNA virus. The HSV is an ancient DNA virus which is widespread in nature and has co-evolved with its hosts. First step of interaction between HSV and its hosts involves the recognition of HS on the surface of the cell. To note, basic structural motifs and modifications of HS glycosaminoglycans seem to have been conserved for several hundred million years of evolution (Cassaro and Dietrich, 1977; Dietrich et al., 1983). HSV attaches to cells by an interaction established between the viral envelope glycoprotein C and cell surface HS (Damonte et al., 2004). As previously stated, CGNs resemble to some extent the naturally occurring GAGs due to their backbone composition of sulfated disaccharides.

Since most pathogens and the toxins they produce bind to specific sugar sequences to initiate infection and disease, it is reasonable to assume that at least some glycan variation must have arisen from this selective pressure (Gagneux and Varki, 1999). On this basis, pressure of selection in vitro with an antiviral drug like HS in the case of HSV may be employed to shorten the time necessary for the appearance of viral variants, particularly attenuated variants (Carlucci et al., 2002).

In view of the variability of viral populations explained above, it is interesting to speculate about the selection of HSV variants by CGNs. Taking into account that HSV is extensively spread in the environment and that this ubiquitous distribution might expose the virus to sulfated polysaccharides, in the form of CGNs, the appearance of virus variants would readily occur as a consequence of an intense virus-CGNs selection. Otherwise, a more heterodox explanation would point to the epigenetic influence on the changes appeared in viral genomes. Irrespective of the hypothesis, our results indicate that attenuation is a common trait of HSV variants arisen after replication in the presence of sublethal doses of CGNs.

4. Isolation of herpes simplex virus variants using carrageenans

Previous studies shown that viral variants of HSV-1 (F strain) and HSV-2 (MS strain) have been obtained through several passages on Vero cells with increasing concentrations of the 1C3 CGN (partially cyclized μ/ν-CGN) and ι or κ-CGNs respectively. Different viral clones were plaque purified and pretested to exclude reversion to wild type (Artuso, 2013; Mateu, 2011). After the viral selection and cloning, all the isolated variants showed a syncytial (syn) phenotype on Vero cells

(Carlucci et al., 2002; Mateu et al., 2011). Variants did not show neither morbidity nor mortality when C57BL/6 mice were infected via intranasal or intravaginal. Nevertheless, the HSV-1 variants were highly lethal for BALB/c mice inoculated by the intranasal route, with a generalized spreading of virus to different organs. Variants exhibited changes at the level of glycoprotein D (gD) (Artuso et al., 2014). These changes have not previously been reported and do not map within the four functional regions of gD (Chiang et al., 1994). This finding is not surprising taking into account that variants are able to induce an altered profile of cytokines and that gD has been pointed out as an inducer of TNF-α (Ankel et al., 1998; Paludan and Mogensen, 2001) and IL-6 (Teng et al., 2005).

Similarly, all the variants derived from HSV-2 were less virulent for mice inoculated either intravaginally or intranasally whereas MS strain produced 100% of mortality. In contrast to HSV-1 variants, the attenuation of HSV-2 variants correlate with high levels of pro-inflammatory cytokines (TNF-α and IL-6) detected in vaginal lavages (Table 1).

An interesting observation is that despite the attenuated phenotype of variants, the levels of infectivity in the site of inoculation do not differ from those observed for the parental strains suggesting attenuation is linked to the immunological response elicited by the variants.

A striking finding is that the susceptibility of variants to CGNs is similar to that of parental virus whereas they show low or middle levels of resistance to heparin, Aciclovir (ACV), and Foscarnet (PFA). This characteristic of the variants is coincident with fact that they show changes at the level of the thymidine kinase (TK) and DNA polymerase (pol) genes (Artuso et al., 2014; Mateu et al., 2016). It has been already reported that alteration at the level of these genes are responsible for changes in virulence of HSV (Andrei et al., 2005).

According to the gene structure of the viral DNA pol (Fig. 1) four mutations were found: A405T, L448F, R500C and Q631K. Two of the changes detected correspond to L448F and Q631K in conserved sites, relevant to the activity of DNA pol. A similar situation occurred with HSV-2 variants (Mateu et al., 2016).

5. Understanding the changes in viral DNA pol by carrageenans

Taking into account that viral envelopes are derived from cell membranes and that the outer membrane of HSV virions may resemble a cytoplasmic membrane from a structural point of view, it is tempting to propose that, as cellular counterparts, viral glycoproteins "connect" the environment with the internal zone of the viral particles. In the model proposed, the glycoproteins of herpesvirus envelope would act as "sensors" of the surrounding medium, i.e. the CGNs, triggering epigenetic mechanisms that enable the virus genome to respond to this particular environment and ensure survival through its replication. The interaction of an HSV glycoprotein, probably gC, followed by a further interaction of gB and gD, with molecules on the cell surface, induces a rapid and highly efficient structural change in the viral tegument which contains non-glycosylated proteins, some of which are critical in the process of viral replication and latency. These proteins can alter the expression of immediate early genes (IE) (alpha), as for example the UL16 protein that is conserved among all herpesviruses and UL48 (Meckes and Wills, 2008, Svobodova et al., 2011). The IE genes encode regulatory proteins and are involved in transcription of the remaining blocks of genetic herpes, early (β) and late (γ). In the β-gene the viral enzymes as the TK and DNA pol and the products of the γ-genes are included (Whitley and Roizman, 2001). It is clear that an alteration in the functioning at the level of proteins of tegument caused by interaction of glycoproteins and CGNs may lead to the expression of an altered polymerase and that variants with mutations at the level of this gene might be positively selected as long as their fitness surpass that of wild type.

Table 1
Characterization of HSV variants obtained by selective pressure with CGN. Viral variants were characterized regarding their phenotype, in vivo virulence, immune response in BALB/c mice and DNA pol and TK genes mutations. The parental strains were also assessed for final comparison.

Characterization	HSV-1 (F)		HSV-2 (MS)	
	Parental strain	Viral variants	Parental strain	Viral variants
Syncytial effect (in vitro)	No	Yes	No	Yes
Intravaginal virulence				
BALB/c	High	Avirulent	High	Low
C57BL/6	Avirulent	Avirulent	High	Low
Intranasal virulence				
BALB/c	High	High	High	Low
C57BL/6	Avirulent	Avirulent	High	Low
Levels of IL-6 and TNF-α	High	Low	Low	High
DNA pol gen mutations	No	Yes	No	Yes
TK gen mutations	No	Yes	No	Yes

6. VirusesViral agents as mediators in "*Élan vital*" of the creative evolution

For Bergson, the main aim of the philosophy is to know the reality, mainly of life. For him, the notion of life mixes together two opposite senses, which must be differentiated and then led into a genuine unity. On the one hand, it is clear from Bergson's earlier works that life is the absolute temporal movement informed by duration and retained in memory. In this case, the philosophy uses intuition by which it captures reality with its intimate essence. For Bergson, life is the product of simultaneous interaction of the intellect, instinct and will. By intuition, humans sympathize with the objects and this allows them to be captured in its interiority, that is, on their inexpressibility. Thanks to intuition the very essence of life that is the duration can be access. But, on the other hand, he has shown that life also consists in the practical necessities imposed on our body and accounting for our habitual mode of knowing in spatial terms. In this manner, science takes advantage from the analysis, a typical operation of the intellect. The analysis is done by concepts, but as these are rigid, the knowledge gained by intellectual analysis (structure of intelligence) put static objects, paralyzes and therefore deforms them. However, accessing to reality this way is very useful, because the purpose is not to know the objects but use them. The key to understanding the two modes for sensing life other than capture the reality is the differential timing between phenomena and the essence of reality. Phenomena move in time physics, in three dimensions that can be separated and stratify in past, present and future. By contrast, the essence of reality, i.e. life, moves on duration. The duration (concrete, real, heterogeneous) is based on memory, understood as a structure of consciousness. For Bergson the only way in which the two senses of life may be reconciled (without being collapsed) is to examine real life, the real evolution of the species, that is the phenomenon of change and its profound causes. To facilitate the understanding of life in its actual duration, Bergson uses a comparison. Imagine a snowball is rolling. At all times its volume increases because a new layer is added, but without losing the previous ones. This can be assimilated to life duration. It is a reality that the past is not lost, but it lasts and acquires new stages of maturity. Bergson says the engine of that progress or evolution is a universal creative impulse called the "*Élan vital*" (Bergson, 1998). Table 2 shows the main points of the philosophy of Bergson, the mechanicism and biological concepts from our system to analyze. We consider that the results shown in this work surpass the explanation capacity of mechanicism and Darwinism.

While the Darwin's theory of evolution is still the greatest breakthrough in biological science, he was unable to explain how this variation occurred. In the 150 years since publication of the Origin of Species, we have discovered three main sources for this variation—mutation, hybridisation and epigenetics. However, the evidence for perhaps the most extraordinary cause of variation was the code for the entire human genome. Not only was the human genome unbelievably simple, but embedded in its code, were large fragments

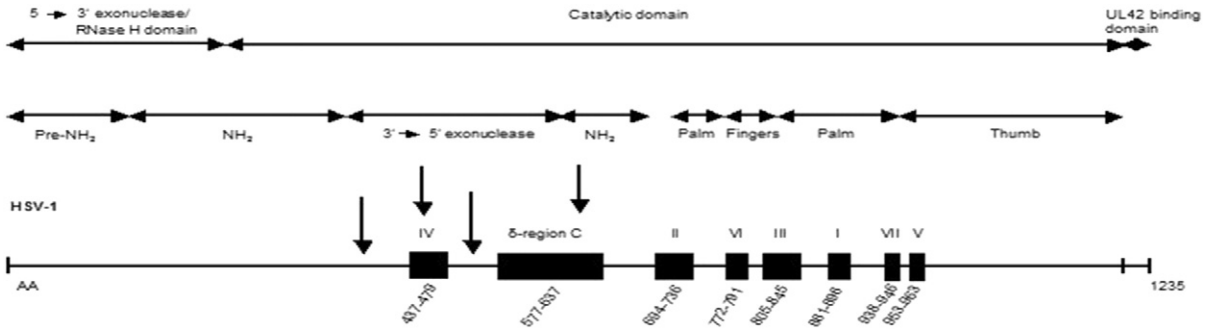

Fig. 1. Regions conserved for UL30 gene of HSV-1 among Herpesviridae genes are shown by black boxes. The roman numbers (I to VII and δ-region C) corresponding to each of these regions are indicated above the boxes. Amino acid (AA) locations are noted below each of these regions for HSV-1.

that were derived from viruses, fragments that were vital to evolution of all organisms and the evidence for a fourth and vital source of variation, viruses (Ryan, 2013).

In our system, the philosophy of Bergson is consistent with inclusive vision of the material and immaterial forces (signals/codes/vital impetus/intuition) that allow us greater understanding of the evolutionary process.

From our point of view, this vital impetus for evolution can be mediated by viruses that are able to generate rapid variability or changes by themselves, according to the environment they are confronted to. Eventually, this variability can be transferred to hosts. This concept is richly discussed by Witzany, that proposes that interaction consortia of endogenous viruses and their defective particles serve as actual key regulators in host cells (Witzany, 2012). They cooperate as complementary tools and act as major sources of "variation".

The ability of all these viral-derived agents to identify correct sequences sites for insertion, deletion, reintegration, recombination, repair and translation initiation, as well as inhibition, support the argument of Manfred Eigen, that the genetic nucleotide sequences of living organisms represent language-like structures and features (Witzany, 2010). However, Eigen failed because he shared the common opinion of the early 1970s, that syntax order in natural languages/codes determines meaning of a given sequence. As we know since Ludwing Wittgenstein "The meaning of a word is its use within a language", it is the context (pragmatics) in which the living agent is concretely interwoven that determines the meaning (function) of a given sequence. Living agents that use natural languages/codes are able to invent de novo sign-sequences as well as reuse sequences parts in novel contextual set up: natural languages/codes emerge through a consortium of interacting living agents that share a limited number of signs (signaling molecules, symbols) and use them according to combinatorial, context-sensitive and content-coherent rules. With this limited number of signs (characters) and limited number of rules an identical sequences can even have contradictory semantics (meanings) depending on the situational context in which a sequences-bearing organism is involved. The most striking example of this adaptive ability is epigenetics. As mentioned above, viruses can act as epigenetic stimuli and as "donors" of genes to living organisms. Also epigenetic forces can select viral populations with better survival possibilities than the parental virus tilting the scale to one or other position in accordance to the conditions of the environment. This "force" would eventually be transformed in viral genetic information to be shared with other living agents. In part, our experiments with HSV and CGNs confirm this hypothesis, at least to explain how perturbation in the surrounding medium can give rise to new viral genetic heritage. In this scenario, viruses may be considered as the "*Élan vital*" of creative evolution.

7. Conclusion

The wide range of symptoms observed for herpesvirus infections is closely related to the complexity and size of the viral genome. Taken into account that this virus has co-evolved with a broad variety of hosts during the evolutive time scale (Carlucci et al., 2011, 2012; McGeoch et al., 2006), it is well probable that differential virulence and persistence do not depend only on the expression of a single gene but on a complex combination of many genes. This slow process can be compared with the rapid emergence of mutants obtained by selection with CGNs, an approach performed at our laboratory to study resistance of the virus to these compounds. One key feature to consider during in vivo HSV evolution is the selective pressure exerted by the immune system that prompted HSV to develop multiple immune evasion strategies. On this line, extensive literature reports changes in gB, gD and gC (Neumann et al., 2003; Friedman et al., 2000; Larcher et al., 2001; Novak and Peng, 2005). Therefore, alterations in these glycoproteins generated by their interaction with polysaccharides might be considered as associated to for the changes in virulence. However, we have also found changes in the genes of TK (Mateu et al., 2011) and DNA polymerase (Artuso, 2013) that have been also reported as related to virulence, replication, and reactivation from latency (Andrei et al., 2005). It could be possible that multi-mutations were selected as a result of the loss of the proof-reading of the viral DNA pol, other genes as gene LAT, UL9 could be altered. Thus, viral QS are endowed with memory of their past intra-host evolutionary (red algae) time, maintained in the form of minority variants (Briones and Domingo, 2008). These variants

Table 2
General concepts of vitalism-Bergson philosophy, mechanism in relation to biological concept and our analysis system.

Vitalism-Bergson's philosophy
1) He postulates that there must be an original common impulse which explains the creation of all living species (living matter); this is his famous "*Élan vital*". While in the inert matter, the "*Élan vital*" has been degraded If the original impulse is common to all life, then there must also be a principle of divergence and differentiation that explains evolution 2) the two main diverging tendencies that account for evolution can ultimately be identified as instinct and intelligence 3) the effort of intuition what allows us to place ourselves back within the original creative impulse so as to overcome the numerous obstacles that stand in the way of true knowledge.
Mechanicism/Darwin
Shows life as a result of the organization of material systems that underlie/It explains of the role of natural selection in driving the evolution of life on earth depend on steady-chancy variation of living things over time.
Biological concept/problem to which it is related
Epigenetics controls the genetic. Epigenetic molecular mechanisms represent a via physical nature giving freedom to manifest in a creative way.
The signals/codes (chemical-CGNs-, vibrational, light, magnetic, biological-VIRUS-, etc.) external participate in the evolution of host.

can re-emerge and some of them might become the preponderant variants in the population of QS that is subjected to selective pressures (CGNs), promote new network formation (virus-host) and may increase our understanding of the genetic and selective force that promote and favoring simbiosis.

This work shows a change of paradigm in the understanding of how a particular compound with a defined target of action (i.e. glycoproteins) can select variants with mutations at other genes. While so far the CGNs have been considered inert and harmless compounds, and under that premise, used in the food industry is not unreasonable to consider the consequences of their ability to interact with the microbiota of the digestive system in the sense discussed in this paper.

Considering that CGNs are involved in primitive defense system of red algae (see Section 3) by reducing the virulence of pathogens, a similar situation may account for the phenomenon observed for HSV variants. On this line, it is tempting to speculate that a similar event might occur with other microorganisms leading to the activation/inactivation of genes that would favor ancestral evolutionary cooperative behavior.

Financial & competing interests disclosure

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