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Review

Virus driven evolution: A probable explanation for "*Similia Similibus Curantur*" philosophy

M.J. Carlucci *, E.B. Damonte, L.A. Scolaro

Departamento de Química Biológica, Laboratorio de Virología, Pabellón 2, Piso 4, Facultad de Ciencias Exactas y Naturales, Universidad de Buenos Aires, Ciudad Universitaria, 1428 Buenos Aires, Argentina

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ABSTRACT

Despite the advances in biomedical knowledge, there remain many challenging and significant unsolved problems among which are included viral pathogenesis and antiviral therapy, as main topics in human health. On this respect, for instance, our knowledge about human immunodeficiency virus and AIDS is still insufficient to deal with problems of immense significance, such as the possible "natural cure" for a chronic infection or the induction of protective immunity against this agent. At the same time, new viral diseases of humans and animals continue to emerge or re-emerge, due to changes in host susceptibility and/or in virus virulence as well as to re-introduction of a virus that had disappeared from a defined population. These changes, at least in part, may appear as a consequence of antiviral therapies and lead to the selection of viral mutants. Moreover, taking into account that viruses have been studied as causative agents of conspicuous diseases a broad spectrum of uncertainty is still present when unapparent persistent infections are considered. Based on Hippocrates (460–357 b.C.E) natural philosophy, "*Natura Morborum Medicatrix*" which represents the natural healing force, i.e.: "Nature cures diseases"; and "*Similia Similibus Curantur*" which means "like cure like", we propose the use of natural compounds with chemical structures similar to cellular membrane components. On this approach, sulfated polysaccharides obtained from marine algae may act as a driving force for the emergence of attenuated viruses, enabling this way a practical approach for preventive therapies for herpes simplex virus infection. At the same time, viruses would be creative tools and their contribution by adding new genetic identity to their host are set points of genesis in the growth of the tree of life.

Contents

1. Introduction

Evolution may be considered as "the process by which the genetic structure of the population of an organism changes with time" with "its actors. . .forever changing and adapting to crisis after crisis but never getting anywhere". In this definition, the expression "never getting anywhere" may be interpreted as a continuous adaptation process driven by the changing conditions of the environment that force the actors to adjust at a pace set by nature. However, Campbell (1993) exhorts us to search for "new" evolutionary mechanisms and strategies that although being present since the very beginning of life come into light everytime

* Corresponding author. Tel.: +54 11 4576 3334; fax: +54 11 4576 3342.
E-mail address: majoc@qb.fcen.uba.ar (M.J. Carlucci).

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we are able to acknowledge their consequences on life. Viruses play a relevant role in these new evolutionary mechanisms by transferring of genes to and from the hosts they parasite (Villarreal and Witzany, 2010). Over the past three decades, it has become apparent that viruses are ubiquitous, abundant and ecologically important in the environment (Breitbart and Rohwer, 2005). As phylogenetic analysis shows, nearly all organisms of all kingdoms have become infected by viruses since the beginning of life. The great impact that viruses can have on the genetic systems is well illustrated by the evolution of mitochondria. As Gray and Lang (1998) have shown, the existence of a strong selection pressure has pushed for the replacement of cellular enzymes by viral ones in mitochondria and chloroplasts. In both organelles, this replacement has been associated with profound modifications in the mechanism of DNA replication and chromosome structure (Forterre, 2006). The fact that viruses are probably very ancient allows to better understanding their extraordinary diversity, explaining why most viral proteins inferred from genome sequencing have no cellular homologues (Daubin and Ochman, 2004). Besides, the existence in the biosphere of an unlimited reservoir of viral proteins has provided opportunities at different steps of the evolutionary process, to introduce new functions into organisms. At the present, it remains controversial the inclusion of viruses in the "tree of life". Several authors assume viruses are non-living organisms and believe their properties are driven solely by thermodynamically spontaneous reactions while others give priority to the fact that phylogenetic tree is based on the genomic content of its components, not the physical manifestations of these genomes. Moreover, the fact that viral genomes carried inside virions encode gene products that allow for adaptation and response to changing intracellular and extracellular conditions favors the inclusion of these agents in the tree of life (Hegde et al., 2009; Ludmir and Enquist, 2009).

Ten thousand years ago, a change in human lifestyle gave rise to "new" viruses we have struggled to control ever since. Our immune system has learnt to cope with these infections, which have subsequently become less severe over the years. But it has been a slow process and, during the adaptation millions of lives have been lost. It should be emphasized that this process arises as the result of the combination of pathogen virulence factors as well as host genetic or immune system factors, not simply or mostly the former. Nowadays, the success of man in the battle for survival together its pursue of dominance and supremacy has inevitably disturbed ecosystems and this is directly responsible for the recent rise in "new" or emerging viral infections like AIDS. Because they are unfamiliar to us, "new" virus infections are often lethal and highly contagious. The situation will only change for the better if we redress the balance and restore the harmony with our surroundings. Viruses by their very nature will unashamedly exploit all opportunities that arise for their own purposes, so we will have to temper our behavior if we want to avoid new and unpredictable conflicts in the future (Crawford, 2000).

2. How are viruses, algae, and animals related?

The discovery that viruses are highly abundant in natural waters initiated renewed research on the impact of viral infection and lysis on aquatic microorganisms (Bergh et al., 1989). The estimation of viruses in different aquatic environments ranges from 10^4 to 10^8 particles per ml. Every second, approximately 10^{23} viral infections occur in the ocean. These infections are a major source of mortality, and cause disease in a great variety of organisms, from shrimp to whales (Van Etten et al., 1991; Wommack and Colwell, 2000; Suttle, 2007). As a result, viruses influence the composition of marine communities and are a major force behind biogeochemical cycles. Each infection has the potential to introduce new genetic information into an organism or progeny virus, thereby driving the evolution of both, host and virus. Although local viral diversity is extremely high, viruses appear to be moving between environments, which constrains total global viral diversity and provides a route for horizontal gene transfer (Breitbart and Rohwer, 2005).

Likewise, the eukaryotic algae represent the oldest known eukaryote for which there exists clear geological data (Knoll, 1992). It appears that all classes of eukaryotic algae have DNA viruses. As expected, the highest genetic richness corresponds to phages. Interestingly, the second largest viral group corresponds to that containing mimivirus and three related algal viruses. These algal viruses are members of the Phycodnaviridae family. Phycodnaviruses are species-specific and will differentiate among strains and subspecies of algae by an unknown mechanism (Mueller et al., 1996; Villarreal, 1999). Interestingly, the genus Chlorella (the unicellular asexual green algae) will resist phycodnavirus infection when it is within its paramecium host (Van Etten, 1994). A well-studied member of this family is the Paramecium bursaria Chlorella virus 1 (PBCV-1), which is unusual among DNA viruses in that it codes for the enzyme hyaluronan synthase (DeAngelis et al., 1997). This is an outer membrane bound enzyme linked to polysaccharide, closely associated with all higher animals and some pathogenic bacteria. Some culturing and molecular studies have found that viruses move between different biomes (Breitbart and Rohwer, 2005), so the presence of these genes in this DNA virus suggests one way in which such a complex phenotype might be able to move during evolution between organisms. In addition, the DNA polymerase sequences of the phycodnaviruses show clear similarity to the herpesvirus and other eukaryotic viral DNA polymerase genes (poxvirus, baculovirus, African swine fever) (Chen and Suttle, 1996). The ancient family of herpesviruses is incredibly widespread in nature. These and other viruses have diverged and evolved with their hosts over a similar time frame (Ewald, 1994). For herpesviruses of mammals, a robust phylogenetic tree has been constructed, which shows many features characteristic of synchronous development of virus and host lineages over large evolutionary time spans. It has also emerged that three distinct groupings of herpesviruses exist: the first containing viruses with mammals, birds and reptiles as natural hosts, the second containing viruses of amphibians and fishes, and the third consisting of a single invertebrate herpesvirus. Within each of the first two groups, the genomes show clear evidence of descent from a common ancestor, but relationships between the three groups are extreme remote. Detailed analyses of capsid structures provide the best evidence for common origin of the three groups. At a more detailed level, the structure of the capsid protein and a capsid shell protein further suggests an element of common origin between herpesviruses and tailed DNA bacteriophages, respectively (McGeoch et al., 2006).

3. Host versus virus?

It is tempting to postulate that the driving forces of evolutionary novelty are not randomly derived from chance mutations of the genetic text, but from a precise genome editing by omnipresent viruses (Witzany, 2006). For decades, non-coding regions of the genome have been ignored or declared as "junk"-DNA. Recently, scientists have realized that these regions incorporate decisive higher-order regulatory functions. New research has shown that these non-coding repetitive sequences originated primarily from retroviral RNA (Villarreal, 2005; Ryan, 2006).

For a long time, viruses were interpreted as causing an acute infection of the host organisms, using the host cellular machinery to reproduce, and achieving their lytic nature only in order to infect other cells. Although this narrative remains valid, it merely

represents a case of viruses that were unable to reach persistent or chronic status of infection (Villarreal, 2005). Most viruses, however, are stable, persistent agents that are able to establish a complex relationship with the host cell and in many cases this interaction lasts for the entire lifespan of the cell even when a competent immune system is present. The immune system is of crucial importance in defense against infection. It has to cope with a large number of different pathogens that relentlessly develop new ways to avoid recognition or elimination. Yet most infections are cleared. Immune-system genes must evolve to keep pace with increasingly sophisticated evasion by pathogens. To remain effective defense demands creativity and competition because many pathogens have sophisticated and rapidly evolving evasion mechanisms, some of which employ mechanisms not too dissimilar to those of the host (Trowsdale and Parham, 2004). This defense response is triggered by the presence of pathogens within the host, however there exists an immune response that comprises a set of autoreactive "natural antibodies" that do not rely on exogenous antigen stimulation to be synthesized by autoantibody-secreting B lymphocytes (Kohler et al., 2003; Ochsenbein et al., 1999). On the other hand, these autoreactive natural antibodies are reactive against components of the host's immune system (i.e. cytokines) and exacerbate ongoing infectious diseases or predispose host to infection (Maddur et al., 2010; van de Vosse et al., 2009).

Individual resistance to pathogens depends on the combination of receptors on cells from the immune system although non-immune genes also influence resistance (Danilova, 2006). Signs of natural selection in a human population are especially illustrative, when a mutation in a certain gene is dangerous in normal conditions but confers resistance to infections widespread in the region. Among the better known are the mutations in hemoglobin and glucose-6-phosphate-dehydrogenase affecting red blood cells and conferring resistance to malaria (Bamshad and Wooding, 2003). Another example is the deletion at the 5′end of the CCR5 chemokine receptor conferring resistance to HIV infection. This molecule serves as the principal co-receptor, with CD4, for HIV-type 1. The allele with the deletion was intensely selected in Europe probably because it also provided resistance to plague and smallpox (Galvani and Slatkin, 2003). More subtle, but nonetheless important, relationship between cell and virus is that associated to changes in cell physiology due to viral infection that regulates cell death, transformation, secretory pathways, cell stress response, etc. (Bureau et al., 2001; Munir, 2010; Shadan and Villarreal, 1993; Villarreal, 2009). This panorama may account for a "symbiotic evolution" of cell and virus, although viruses have much shorter generation times than cells. Studies of genomic polymorphism of herpes simplex virus type 1 (HSV-1) suggest that the evolution of HSV-1 would be very slow and host-dependent (Sakaoka et al., 1994).

4. The construction of the evolution process

Goethe's Faust appropriately express "Im Anfang war die tat" (In the beginning was the deed), so the "deed" never was invented (invent derive from latin "invenire" mean to find), was fulfilled, then came the thoughts which are a relatively late discover of man. As supported by Charles Darwin's theory (1859) "On the Origin of Species" the conscious of man was developed slow and laboriously in a process that needed countless eras to reach the civilized state (Jung, 1964). As Wilber (1996) explained a consciousness evolves and unfolds, each stage solves or diffuses certain problems of the previous stage, but then adds new and recalcitrant (and sometimes more complex and more difficult) problems of its own. Precisely because evolution in all domains (human and otherwise) operates by a process of differentiation and integration, then each new and more complex level necessarily faces problems not present in its predecessors. Dogs get cancer; atoms don't. So evolution inherently means that new potentials and new wonders and new glories are introduced with each new stage, but new fears, new problems and new diseases invariably accompany them.

Precisely because evolution proceeds by differentiation and integration (each level is a whole that is part of another whole, indefinitely, like whole atoms are parts of molecules, whole molecules are parts of cells, which are parts of complex organisms and so on), something can go wrong at each and every stage, then more disease there can be. And one of the most prevalent forms of evolutionary pathology occurs when differentiation goes too far into dissociation. In human evolution, for example, it is one thing to differentiate the mind and body, quite another to dissociate them. One thing is to differentiate the virus from cell, quite another thing is to dissociate them. Differentiation is the prelude to integration; dissociation is the prelude to disaster.

5. Relations between glycosaminoglycans, carrageenans and viruses

Glycosaminoglycans (GAGs), long unbranched polysaccharides consisting of a repeating disaccharide unit, constitute a considerable fraction of the glycoconjugates found on cellular membranes and in the extracellular matrix of virtually all mammalian tissues. Examples of GAGs include heparan sufate (HS), heparin, dermatan sulfate and condroitin sulfate. HS, a highly sulfated polysaccharide (SP), tends to be emphasized as most biologically active GAG. The sulfated monosaccharide sequences within heparan sulfate determine the protein binding specificity and regulate fundamental biological functions including growth control, signal transduction, cell adhesion, hemostasis, morphogenesis, lipid metabolism and pathophysiology (Esko and Sellect, 2002). Numerous viruses (including herpesviruses) and parasites utilize cell surface HS as receptor to infect target cells. Recent studies revealed that HS plays multiple roles in assisting viral infection, and the activities in promoting viral infections require unique monosaccharide sequences, suggesting that HS could serve as a specific receptor for viral infection (Liu and Thorp, 2002). The herpes simplex viruses attach to cells by an interaction between the envelope glycoprotein C and cell surface HS. The virus–cell complex is formed by ionic interactions between the anionic (mainly sulfate) groups in the polysaccharide and basic amino acids of glycoprotein, and non-ionic ones depending on hydrophobic amino acids interspersed between the basic ones in the glycoprotein-binding zone (Damonte et al., 2004). This interaction is a decisive step in virus multiplication and, as mentioned above, may be differentiated but not dissociated from an evolutive point of view.

Likewise, carrageenans (CGNs) are high molecular weight SP derived from several species of algae, known as red seaweeds (Fam: Rhodophyceae). CGNs are used by the food and pharmaceutical industries and as an ingredient in pharmaceuticals and personal care products. CGNs resemble to some extent the naturally occurring GAGs owing to their backbone composition of sulfated disaccharides are believed to be of potential therapeutic importance because they can mimic with GAGs present in cell membranes.

6. "*Similia Similibus Curantur*"

One can easily find that methods of orthodox medicine act according to one of Hippocrates principle "contraria contraribus curantur", when the basic principle of homeopathy, one of non-conventional therapy, is the other Hippocrates one "*Similia Similibus Curantur*".

A pathogen could be defined as an organism capable of colonizing a host where the interaction results in disease for the latter (Brown et al., 2006). Then, virulence or pathogenicity refers to the ability of a virus to cause disease in an infected host. Host–pathogen relationships resulting in severe disease (i.e. high virulence) may be considered as relatively young in evolutionary terms and evolve eventually towards a balanced state of mutualism (Alexander, 1981). On this scenario, at first sight, virulence would benefit the pathogen in the host–pathogen relationship however, attenuation would fulfill host and virus requirements when prolonged instances of interaction are considered (Ewald, 1983; Wickham et al., 2007). 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 attenuation. Moreover, in this last case and based on the principle "*Similia Similibus Curantur*" we may speculate that if herpesviruses which are extensively spread in the environment are exposed to SP (its natural receptor), in the form of CGN, the appearance of the attenuated virus variants would readily occur as a consequence of an intense virus–host (CGN would be the host in this case) interaction. We have performed plenty of investigation based on the antiviral activities of CGN against herpesviruses in mammalian cells and animal models (Carlucci et al., 1997, 1999a,b, 2002) however our recent goal focussed on the results obtained when virus passaged in the presence of increasing concentrations of CGN was characterized. These results revealed that increasing the inhibitory concentration 50% of the CGN in successive passages of HSV-1 and HSV-2, attenuated strains, avirulent for mice inoculated by intravaginal or intranasal route were readily obtained. (Artuso et al., 2009; Mateu et al., 2010).

Not only the environment would be a suitable scenario for HSV evolution. It was recently reported that HS is lived in soluble fragments during the course of inflammation, infection and tissular damage (Ihrcke et al., 1998). In healthy tissues, no significant fractions of soluble HS are found, but the concentration observed in damaged tissues or in the urine of infected individuals is enough to stimulate dendritic cells (Kainulainen et al., 1998; Oragui et al., 2000). Besides, CGN extracted from red seaweed has been used in food products for centuries and was patented as a food additive for use in the United States in the 1930s. It has also been used as a laxative, as treatment for peptic ulcer disease, and as a component of pharmaceuticals (Klose et al., 1968; Moirano, 1977). It means that these types of viral variants may arise spontaneously as consequence of structural similarities between SP and cellular HS.

A next goal will be to compare and unify genomes, gene sequences and gene sets from such sets of variants to discern major events in the evolutionary history or to anticipate the emergence of future viral diseases (McGeoch et al., 2006).

7. Conclusion

We may say, in accordance with the most accepted theory among physicists, that the acquisition of information (i.e. knowledge) consumes energy leading to augment global entropy within the system. Assuming that entropy measures the physical disorder of a system and that it might be associated to the amount of information in the system it is tempting to speculate that chaos would be a sign of the presence of a certain amount of information in the system. The simple idea used as a base for the Prigogine's research: the disorder is not the "natural" state of the matter, but, on the contrary, a step to precede an uprising of higher order. On the premise that evolution is related with the Natural Dynamic Order, the matter evolves to life and the life evolves to a major state of consciousness and biological information. On this scenario, pathogenic viruses would be agents out of natural order (environment, host, species, homeostasis, etc.) to cause a temporary, persistent, moderate or fatal chaos as a consequence of the new information received by the host. The ancestral concept "*Similia Similibus Curantur*" defines a strategy to restore host–pathogen balance, by using attenuated viral variants. In the case of HSV, syncitial variants obtained by a selective pressure with a sulfated polymer that has a similar structure to GAG are prospective tools for anti-HSV or gene therapy and prophylaxis.

"Now, Homo sapiens has developed the facility to design his and other species's evolution towards preconceived goals deliberately. . .Ask not what evolution can do for a species but what a species can do for evolution!" (Campbell, 1993).

8. Future perspective

This work invites us to think about a possible alternative to attenuate virus for basic science study, therapeutical or prophylactic applications, employing natural compounds with chemical structures already "seen" by the pathogen and present in the host as essential cellular components widely distributed in nature. This strategy could be considered as a natural evolutionary process where the virus contributes with valuable "updated" information gathered from previous ancestral infections and making it available for "new" actual hosts, generating a reciprocal benefit between host and virus.

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Conflict of interest statement

The authors do not have any conflict of interest.

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