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Viruses of the Archaea: a View on the Viral World from the Perspective of Hyperthermophilic Viruses

David Prangishvili

Foreign Member of the Georgian National Academy of Sciences; Institut Pasteur, Department of Microbiology, 25 rue du Dr. Roux, 75015 Paris, France

ABSTRACT. The views on the nature and evolution of viruses are changing in recent years as a result of the advances in environmental virology and the characterization of a plethora of novel viruses of microorganisms. One intriguing group of novel viruses infects hyperthermophilic members of the Archaea, a domain of life different from the Bacteria and Eukarya. Twenty-two archaeal DNA viruses isolated and characterized by us from extreme geothermal environments in Europe, North America, and Asia reveal exceptional diversity of unique morphological and genomic features. Studies of the members of this viral group provide new perspectives on the world of viruses. Here I briefly summarize our results and speculate on their impact on the ideas on the nature, origin and evolution of viruses, leading to the notion on a virus as an organism existing in a latent state as a virion or a provirus, and in a productive state as a virion factory. Besides, I advocate the concept that precursors of cells and viruses have co-evolved from ancestral forms of life, and that the lifestyles of viruses, their genomic diversity and the variety of their genetic cycles are chronicles of different stages of this co-evolution. *© 2011 Bull. Georg. Natl. Acad. Sci.*

Key words: *virus, archaea, hyperthermophile, origin of viruses, evolution of viruses.*

The evolution of notions on the nature and origin of viruses

The word "virus" is known to be first used by Celsus in the 1st century A.D. referring to the poisonous agent, "venenum", causing rabies in dogs [1]. Throughout centuries the word was used to denote generally a poisonous agent. In the 19th century, with the awareness of the existence of transmittable diseases, it acquired a meaning of an infectious agent. More precise definition appeared at the end of the 19th century and was linked with the experiments of Ivanovski [2] and Beijerink [3] who have shown that the causative agent of the tobacco mosaic disease, an ultra-microscopic virus, was small enough to pass through the pores of filter candles impermeable to bacteria. Ivanovski, failing to confirm his original idea that a virus is a microbe of an extremely small size, suggested that it may be a kind of toxin. However, Beijerink showed that the virus multiplied in infected tissues and therefore could not be a toxin. He considered virus not as a cellular structure but rather to be liquid in nature, a *contagium vivum fluidum* (soluble living germ), a soluble molecule able to replicate but only when "incorporated into the living protoplasm of the cell". Such view of a virus, as a pathogenic molecule that incorporates in the host cell and borrows its metabolic and replicating mechanisms for its own purposes, is astonishingly close to the modern concept of the virus. However, it was not widely accepted and dominant was the view that a virus is a very small, ultra-microscopic microbe differing mainly in size from its more conventional counterparts. Gradually, the number of filterable agents recognized as viruses was growing and included e.g. causative agents of foot-and-mouth disease and yellow fever [4]. This necessitated their classification based on common biological factors rather than mere size and a definition of a virus as an ultramicroscopic obligate parasite was introduced.

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The discovery of bacterial viruses (1915-1917) supported the view that viruses are particulate parasitizing entities. Without any doubt in the nature of his discovery, D'Herrele formulated a view of bacteriophages as independently living and multiplying predators on bacterial cells – bacteria eaters, hence the name "bacteriophage" [5]. However, this view was strongly debated and some influential opponents claimed that bacteriophage represents bacterial enzyme that stimulates its own production [6], referring to the original interpretation by Twort of his observations on bacterial lysis by viruses [7]. The discovery of the complex phenomenon of the bacterial lysogeny brought even more confusion in the development of the concept of the virus [8].

Successful crystallization of tobacco mosaic virus (TMV) in 1935 by Stanley [9] revealed virus as a chemical object, fundamentally different from cellular organisms. However, the result dramatized rather than resolved the question whether viruses are alive and undermined the boundary between living and non-living entities. Moreover, presuming that a virus is a molecule, it was thought that a study of virus replication would be a promising approach to understanding gene replication. By the legendary group of phage researchers, the "Phage group" and associates, bacteriophages were selected as model viruses for such studies; their remarkable success is well known [10]. As a result, it finally became possible to arrive at the definition of a virus as an organized particle containing either DNA or RNA but not both, and reproducing itself from its own endogenous material within a living cell, by using existing mechanisms of that cell [10]. This view on viruses is still the one most broadly accepted. In the most recent Dictionary of Virology viruses are defined as "Infectious units consisting of either RNA or DNA enclosed in a protective protein coat; viruses are not organisms" [11]. However, in recent years it has been proposed to avoid the conventional focusing on viral particles in the definition of a virus, and to conceptually identify virus with its intracellular form [12]. During their life cycle, some eukaryal viruses, e.g. the Mimivirus of amoeba, replicate within cells in particular structures with defined borders, called virus factories, which were suggested to represent a genuine nature of a virus [13]. The perception to consider a viral factory as a real viral organism led to the definition of viruses as capsid-encoding organisms, different from the ribosome-encoding organisms (bacteria, archaea, and eukarya) [14] and to the introduction of the virocell concept, as the recognition of the fundamentally cellular nature of viruses [15].

The evolution of ideas on the nature of viruses determined theories on their origin. In the earlier years when viruses were regarded as ultra-microscopic parasitic microbes, it was thought that they may have originated from cellular organisms by reductive evolution. The reduction hypothesis is still considered today and suggests that viruses may have once been small cells that parasitized larger cells, and eventually their dependence on parasitism has caused the loss of genes that enabled them to survive outside a cell. Major critics of this theory were members of the "Phage group", whose strongest argument against the hypothesis was the non-cellular organisation of viruses and the nature of their capsids which is morphologically analogous to cellular organelles made up of protein subunits rather than to cellular membranes. For the Phage group, with their approach to identify viruses with genes, the escape hypothesis became the paradigm for explaining the origin of viruses. It was suggested that viruses originated from fragments of cellular genomes and represent an assemblage of genes which escaped the cell and learned to be independent. The hypothesis was consistent with the recognition of the phenomenon of the lysogeny and the discovery of bacterial prophages, viral genomes integrated into chromosomes. After the discovery of mobile genetic elements the escape hypothesis became even more popular. In addition to the two above-mentioned hypotheses ("reduction" and "escape"), it is considered that viruses might have originated in the pre-cellular world (see, e.g. [16]).

Viruses back on stage in the 21st century

Environmental virology studies are changing our view on the role of viruses in the Biosphere [for reviews, see refs. 17,18]. Enumeration of virus particles in different environments by florescent staining revealed the astonishing abundance of viruses on our planet. It has been estimated that globally there are 10^{31} virus-like particles. Since the average half-life of free viruses in most ecosystems is about 48 h, an estimated 10^{27} viruses are produced every minute. This means that roughly 10^{25} microbes die every 60 seconds due to viruses. These estimations, in their turn, helped to realize that viruses are important microbial predators that influence global biogeochemical cycles and are responsible for a significant part of the mortalities and nutrient recycling in most environments.

In addition to their influence on biogeochemical cycles, viruses drive microbial evolution by natural selection for microbes resistant to infection and via lateral gene transfer. Many viruses are strain-specific predators. Therefore as a particular microbial strain becomes dominant in a system, the number of its viral predators will increase exponentially and kill it off. This will leave a niche for another microbial strain to grow into, which will be subse-

quently killed off by another viral type. This means that the dominant microbial species within a system will be constantly turned over. This "kill-the-winner" hypothesis may explain much of the observed microbial diversity and changes in community structure.

Viruses are also important exchangers of genetic information between hosts, because they inject their genomes in the host cells. For example, most of the completely sequenced cellular chromosomes contain proviruses, i. e. viruses that have integrated their genomes into the host's chromosome and are replicated as a part of cellular genomic DNA. Most proviruses can become active at a later date and subsequently end up killing their host. Acquisition and loss of proviruses is one of the most common mechanisms of lateral gene transfer.

All these revelations required revision of the conventional view on viruses as insignificant elements of the biosphere. However, the importance of the role of viruses in the biosphere is being acknowledged with great difficulty, apparently due to a strong tradition of contemplating viruses as by-products of evolution and refusing to consider them as living - a remarkable manifestation of the difficulty to revise a scientific concept which has been accepted, entrenched and appreciated. Typical is the statement in one of the most recent books on the origin and evolution of life: "To consider viruses as living creates much useless confusion. Nothing in the definition of life or in the non-living nature of viruses has to be changed to acknowledge the importance the viruses had in the evolution of organisms" [19].

My personal views on the nature of viruses have been formed and evolved in the course of our studies on viruses which are infecting hyperthermophilic members of the domain Archaea. These viruses turned out to form a unique group in the viral world, studies on which provide new perspectives on basic questions of origin and evolution of viruses. To illustrate this, below I will briefly describe our results and ideas developed during their analysis, as well as in the course of stimulating discussions with Patrick Forterre.

What do archaeal viruses tell us about the origin and evolution of viruses?

In recent years, we have isolated and described 22 different new virus species from extreme geothermal environments in Europe, North America and Asia. All these viruses have double-stranded (ds) DNA genomes and infect hyperthermophilic members of the domain Archaea, which grow optimally at temperatures above 80°C (for reviews, see refs. [20-25]). The viruses are so exceptional and diverse in their morphological and genomic properties that they have been assigned to eight different viral families, four of which had to be newly introduced. Moreover, the virion morphologies are surprisingly complex, as exemplified by the *Acidianus* bottle-shaped virus, ABV, a member of the family *Ampullaviridae* [26]. The virion, resembling in its shape a bottle, is so complex that it would be hard even to imagine the existence of a virus of such complexity. Its particle carries an envelope which encases a funnel-shaped core built from toroidally supercoiled nucleoprotein filament (Fig. 1A). The *Acidianus* two-tailed virus, ATV, a member of the *Bicaudaviridae,* has also most unusual morphological features [27, 28]. Its virion is extruded from a host cell as a spindle-shaped particle, which later, extracellularly and independently of the host cell, develops protrusions from the pointed ends, specifically at high temperatures of the natural habitat (Figs. 1B, $1B_1$). We have isolated also viruses with tail-less spindle-shaped virions. They represent the family *Fuselloviridae* which comprises two morphotypes, illustrated by *Sulfolobus solfataricus* spindle-shaped viruses 5 and 6, SSV5 and SSV6 [29], which differ in gross morphology and putative attachment structures (Figs. $1C_1$, $1C_2$). Virion morphotypes of the above-described viral families are unique for the Archaea and have never been observed among viruses of Bacteria or Eukarya.

Unique are also linear viruses with ds DNA genomes characterized by us, which differ from bacterial or eukaryal linear viruses all of which carry either single-stranded (ss) DNA or RNA genomes. Members of one family of archaeal linear viruses, the *Rudiviridae,* including *Sulfolobus islandicus* rod-shaped virus 2, SIRV2 [30], have non-envoloped virions composed of dsDNA and multiple copies of a single protein (Fig. 1D). Members of the family *Lipothrixviridae* have more complex virions; they are enveloped and carry diverse terminal adsorption structures (Fig. 1E) [31]. The termini of the *Acidianus* filamentous virus 1, AFV1, [32] have exceptional claw-like morphology which clamp onto viral receptors located on host cell pili (Fig. 1F); the virion of the *Acidianus* filamentous virus 2, AFV2, [33] has complex collars at the termini with two sets of attached filaments, resembling a bottle brush (Fig. 1G), and there is one long filament attached to the termini of the *Acidianus* filamentous virus 9, AFV9 (Fig. 1H) [34]. A different type of linear virus is represented by the *Aeropyrum pernix* bacilliform virus 1, APBV1, from the proposed family *Clavaviridae* [35]. The short, bacilliform virion is only 140 nm long, and has asymmetric ends, one of which appears to be rounded and another one pointed (Fig. 1I). The *Aeropyrum pernix* ovoid virus 1, APOV1 (Fig. 1J), with slightly pleomorphic ovoid virions is the proposed member of the family *Guttaviridae*,

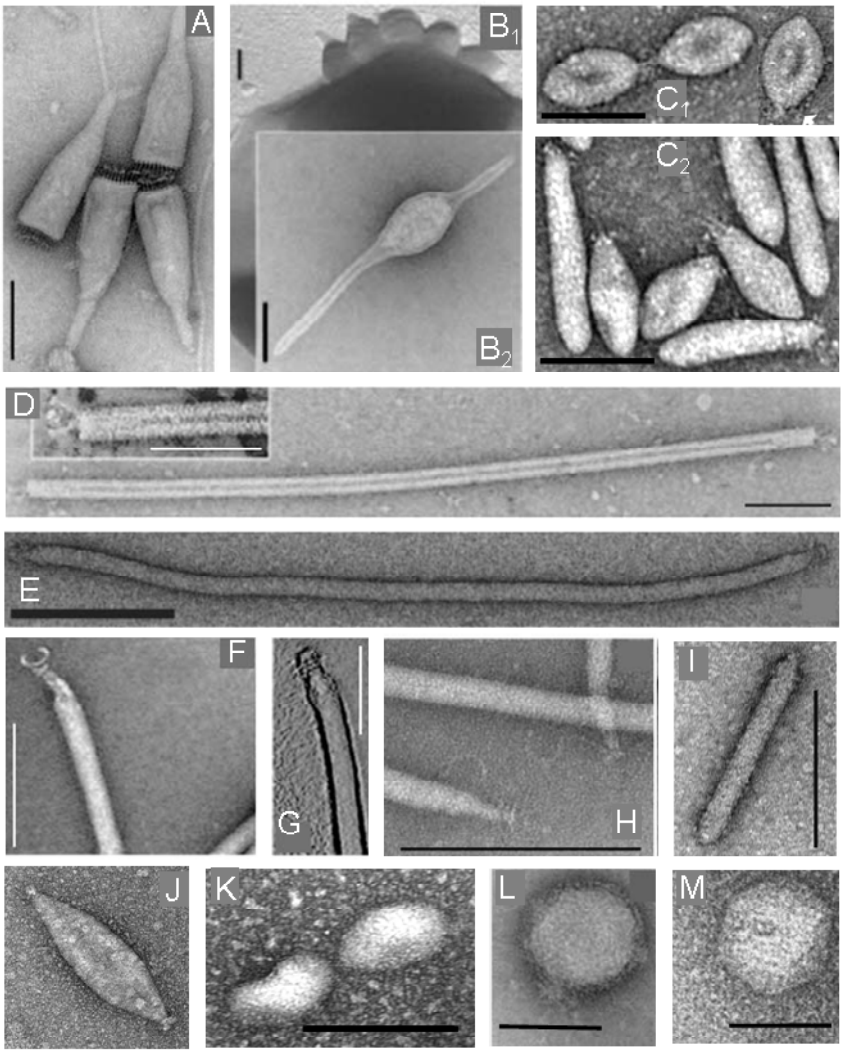

Fig. 1. Negative contrast electron micrographs of viruses of hyperthermophilic archaea, representing different families. (A) *Ampullaviridae*: ABV; (B and B_1) *Bicaudaviridae*: extrusion of ATV from a host cell, and a mature form of ATV virion; (C_1, and C_2) *Fuselloviridae*: SSV7 and SSV6; (D) *Rudiviridae* : SIRV2; (E) *Lipothrixviridae*: AFV3; (F, G, H), *Lipothrixviridae*: terminal structures of virions of AFV1, AFV2, and AFV9, correspondingly; (I) *Clavaviridae*: APBV1; (J) unclassified APSV1; (K) *Guttaviridae*: APOV1; (L) *Globuloviridae*: PSV; (M) unclassified : STIV2. Scale bars, (A-D, I-M) 100 nm, (D - inset, F, G) 50 nm; (E) 200 nm; (J) 60 nm. Modified from [refs. 26-38].

and the *Aeropyrum pernix* spindle-shaped virus 1, APSV1 (Fig. 1K), has not yet been classified [36].

Among viruses studied by us are also spherical viruses of two types. One type is represented the *Pyrobaculum* spherical virus, PSV, a member of the family *Globuloviridae* [37]. The virion has a lipid-containing envelope which encases helically arranged nucleoprotein core (Fig. 1L). The other type of spherical viruses is represented by *Sulfolobus* turreted icosahedral virus 2, STIV2 [38]. Its non-enveloped icosahedral virion has inner lipid membrane and carries turret-shaped adsorption structures (Fig. 1M).

The above-described collection of 22 viral species isolated and characterized by us represents 75% of all known hyperthermophilic archaeal viruses. About a dozen species described in other laboratories are assigned to the families *Fuselloviridae, Lipothrixviridae* and *Guttaviridae* (for review, see refs. [22, 25]). Not only morphotypes but also genomes of the hyperthermophilic archaeal viruses are unique. More than 95% of their genes do not have homologues in databases (except in other hyperthermophilic archaeal virus) [39].

A failure to understand encoded functions could be partly due to unknown, exceptional features of the life cycle of these viruses. The existence of such features was indeed revealed in the course of studies on interactions of the rod-shaped rudivirus SIRV2 (Fig. 1D) with its hyperthermophilic host *Sulfolobus islandicus* [40]. Shortly

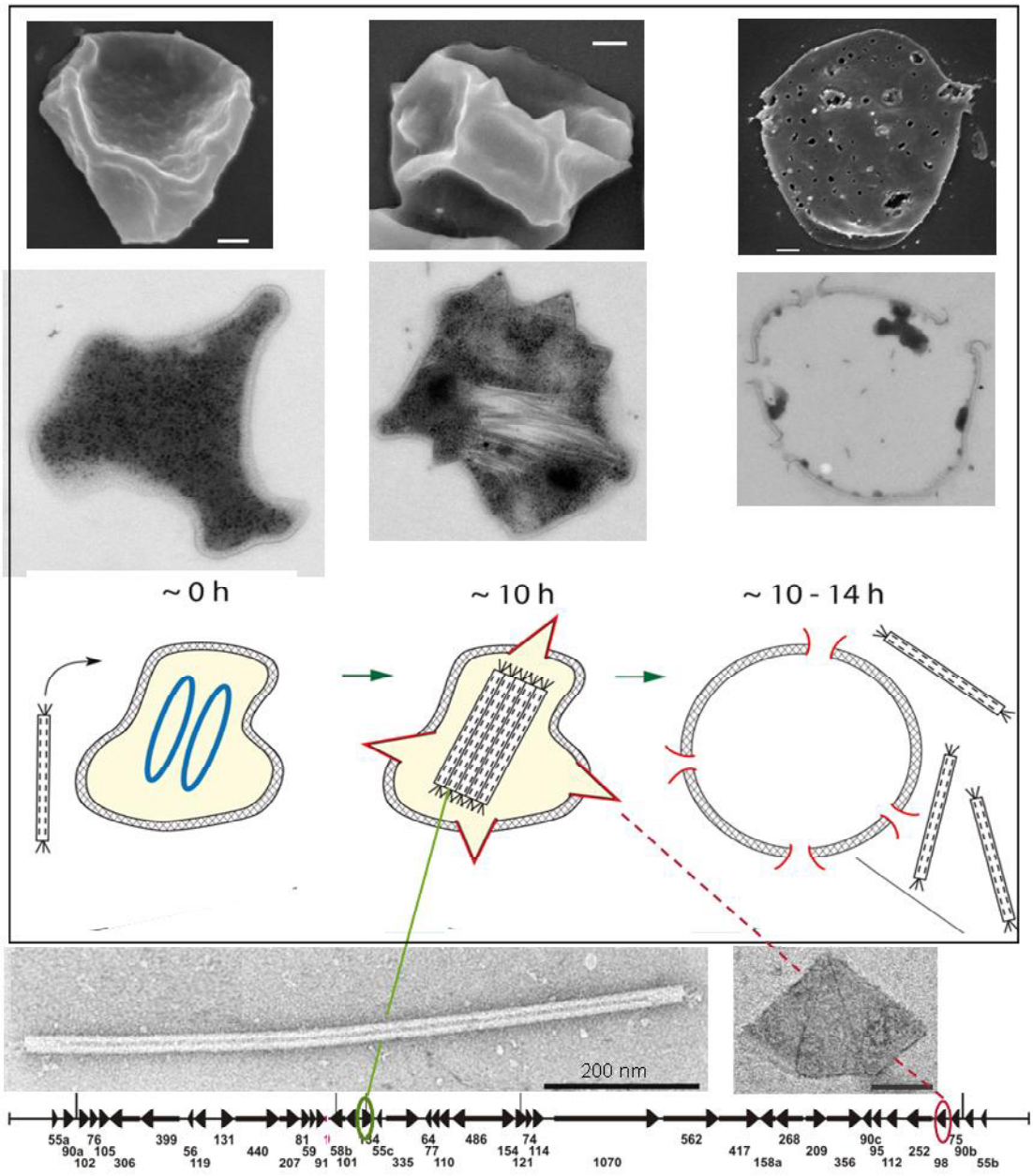

Fig. 2. Intracellular life cycle of the virus SIRV2. Framed are scanning electron micrographs (upper row), negative contrast electron micrographs of thin sections through infected cells (middle row), and schematic representation of intracellular stages (lower row) at 0, 10, and 14 hours post infection. Below the frame there are shown negative contrast electron micrographs of the virion and virodome of SIRV2, and the viral genome map with indication of genes encoding the major capsid protein and the virodome protein. Modified from [refs. 40-42].

after infection, large pyramidal virus-induced protrusions, VAPs, are formed on cell surface (Fig. 2). Their formation coincides with the massive degradation of the host chromosomes, intensive replication of viral genome and self-assembly of virions. Eventually, the VAPs open outwards, thus creating large apertures through which virions escape the cell (Fig. 2). This virus release mechanism is unprecedented in virus biology and significantly differs from the cell lysis strategies of bacterial and eukaryal viruses. The VAPs could be extracted from the membrane fraction of infected cells as stable independent formations [41]. Same as *in vivo*, they represent hollow pyramids with 7-fold symmetry (Fig. 2). The only component of the VAPs is a 98 amino acid protein encoded by the virus, able to self-assemble into hollow pyramidal structures [41]. Thus, the virus SIRV2, for its life cycle, in addition to the capsid encodes one more type of structural formation, the VAP.

To sum up, the existing data allows to conclude that DNA viruses of hyperthermophilic Archaea are fundamentally different on morphological and genomic levels

from the viruses of Bacteria and Eukarya. Considering also profound morphological and genomic differences between DNA viruses of Bacteria and Eukarya, we are facing the situation when each of the three domains of life appears to have its own collection of associated DNA viruses.

Although generally profoundly different, some molecular characteristics of viruses from three domains retain a trace of common ancestry [43]. This concerns e.g. protein-primed DNA polymerases which are homologous in the archaeal virus ABV, the bacterial tectiviruses and eukaryal adenoviruses [44]. Another example of such shared molecular traits is presented by remarkable similarity of crystal structures of the major capsid proteins of the icosahedral archaeal viruses STIV/STIV2 [38], bacterial tectiviruses and eukaryal nucleo-cytoplasmic large DNA viruses [45]. All these capsid proteins carry the "double jelly-roll" fold. The existence of these shared traits could hardly be due to the cross-domain spreading: profound differences in molecular organisation of archaeal, bacterial and eukaryal hosts would have been a major obstacle for the transfer of viruses between the three domains. It seems also hardly possible that the similarities in molecular characteristics result from convergent evolution. The existence of these similarities is most consistent with the concept of primordial gene pool as a source of viral genes, with the origin of the shared features in the virosphere that predated the divergence between the Archaea, Bacteria, and Eukarya.

If viruses predated the emergence of the three domains of life, why should there be major differences between the viruses of Archaea, Bacteria, and Eukarya? One possibility is that the three pools of viruses, partly overlapping, were selected from the ancient virosphere when the three domains emerged, and that these viruses subsequently coevolved with their hosts [22, 25].

The morphological diversity and complexity of hyperthermophilic archaeal viruses is astounding, especially considering the modest number of known species which may represent only the tip of an iceberg. This diversity and complexity appears to be hardly compatible with the view on viruses as derivatives of modern cells, as suggested by the reduction hypothesis on virus origin. The succession of events which would be required for reducing a cell into all these types of virus particles is hardly imaginable. The structural complexity of archaeal viruses is neither compatible with the escape hypothesis. It is difficult to explain how and why the genes which escaped modern cells could elaborate such complex, sophisticated solutions for their packaging, as e.g. in the case of the bottle-shaped or fusiform viruses. However, the major argument against the escape hypothesis is the extremely high proportion (95%) of viral genes of unknown function that do not match known database entries and do not have cellular homologues.

The negation of both the reduction hypothesis and the escape hypothesis implies a presumption of a cell-independent origin of viruses (or at least their descending from hypothetical extinct cellular lineages [43]). One possibility to reconcile such presumption with the fact that the same genetic code and overall nucleic acid copy mechanisms are exploited by viruses and cellular life forms is to postulate that the basic principles of life have co-evolved in these two types of biological entities. This does not necessarily imply that the ancestors of one type of the biological entity has preceded the ancestors of the other, both could have been derived in concert from a common ancestral form of life. Such scenario would explain the success of the viruses on our planet: their amazing abundance and the remarkable diversity of viral genomic content and genetic cycles.

If ancestors of viruses and cells have concomitantly appeared on the planet, then the Biosphere from the very beginning could have been shaped by constant interactions between the two types of entities. The first molecules, the replicators, able to create copies of themselves, had to deal with a paradoxical situation when, from one side, natural selection was favouring high copying fidelity and did not push any changes (nothing actually "wants" to evolve), and, from the other side, copying errors, changes, were essential precondition for the evolution to happen at all [46]. These two modes of replication could have been taken over by two types of intimately interacting replicators, one with more error-prone replication technique than the other, one type responsible for producing errors and the other type favouring stable reproduction. The first could be a prototype of the viral type of biological organisation and life cycle, while the other could have developed into "survival machines [46]" and later into cells. Accepting such view on the origin of life, postulating cooperative evolution of ancestors of viruses and cells in a kind of innovation-sharing symbiosis, it is possible to foresee that the error-prone replication style would be restrictive to the increase of organisational complexity and favour rather expansion of diversity, while survival machines, future cells, responsible for the accurate replication, would evolve in the direction of sophistication and increasing complexity. The establishment of the basic principles of life shared by extant viruses and cells (e.g. genetic code or general principles of nucleic acid replication) could have occurred in this phase of the cooperative union of their ancestors. The

ideas are in line with the notion that from the beginning the evolution was communal and that the innovation-sharing led to the emergence of modern cell designs from a communal state rather than from a shared ancestor [47, 48]. The presently observed phenomenon of persistent viral infections, e.g. by temperate bacterioviruses or the endogenous retroviruses, in the course of which viral genomes become incorporated into host chromosomes or exists as a plasmid, could also have its origin in this "friendly" phase of coevolution of the ancestors of contemporary viruses and cells.

Eventually, the increasing complexity of virus-like and cell-like entities could lead to their evolution into separate types of organisms, viruses and cells, with two different mechanisms for reproduction – through replication of infectious virus particles and through cell division. This, in its turn could have lead to the conflicting situation when each type would be pushing the replication of its own gene content. Starting from this moment, the war between the two types of organisms, viruses and cells, could become a major engine of the evolution in the Biosphere, as it was recently suggested by Patrick Forterre and myself [49]. In the course of this still on-going, billion-year war there exists a strong driving force for viruses to invent new genetic content, in order to overcome constantly evolving defence systems of the host, whereas cells attempt to benefit from these evolutionary novelties by adapting and exploiting them for their own purposes. This war proceeds in the framework of natural selection and involves much stronger evolutionary forces than the conventional "mutation-plus-selection" model. The high potential of viruses for development of evolutionary novelties is an inherent component of their lifestyle, which allows rapid creation and selection of new genes/proteins due to fast replication cycle and high number of the progeny. Thus, in the role of "enemies" viruses can impose extremely high selection pressure on their hosts. On the other hand, the extensive gene flow from viruses to cells provides cells with powerful means to overcome this pressure. The virus-cell war was considered to be a source of such key events as e.g. the origin of DNA and DNA replication mechanisms [50].

What would be a definition of a virus in such perception of the Biosphere? To answer this question, I would like to refer to the above-described results of interaction of the virus SIRV2 with its host *S. islandicus* (Figure 2). The results illustrate an extreme case of viral aggression. The number and extent of elaborate modifications caused by SIRV2 on the host cell are of such magnitude that it can hardly be contemplated as the archaeon *Sulfolobus*. The virus infection results in total disappearance of the cell chromosome. The only genetic information present in the cell is of viral origin, viral genes direct all processes. The virus is in total control of the biological unit which it has appropriated from the cell and modified in accordance with its own purposes, to produce the progeny and release it. The cell surface is modified by specific structures, facilitating virion escape from a cell, the transition from intracellular to extracellular stages of viral life cycle. The whole cell has been transformed into a kind of virus factory, conceptually identical to those built by some eukaryotic viruses inside infected cells, dedicated to viral genome replication, virion assembly and virion release.

As already mentioned, eukaryotic viral factories were suggested to constitute the genuine identity of viruses, which thus might be regarded as a specific type of living organism. A weakness of this concept was the failure to observe viral factories in cells from other domains. SIRV2, as described above, constitutes the first example of an archaeal virus producing a transient viral factory, consisting of the entire transformed infected cell [40]. The consideration of a virus factory, an intracellular state of a virus, as an essential manifestation of its genuine nature leads to the notion on a virus as a concept based on experimental data and rational thought rather than a well-defined entity. By contrast, the virions which represent the extracellular state of a virus are real physical entities produced in the course of biological evolution and should not be excluded from virus definition. An attempt to cover different forms of viral way of life leads to the definition of a virus as an organism existing in a latent state as a virion or a provirus, and in a productive state as a virion factory.

Our ideas on life are changing and viruses are taking a central part on the stage. No matter how we define viruses, no matter whether we consider them living or non-living, it is now unquestionable that viruses are the major component of the Biosphere and that attempts to ignore this circumstance are indefensible in considerations on origin and evolution of life. Without doubt, better knowledge on the diversity of viruses, their genomes, genetic cycles, and mechanisms of interactions with hosts will shed light on different stages of the evolution of the Biosphere from the very beginning, maybe even from the prebiotic period of ancestral forms of life.

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მიკრობიოლოგია; ვირუსოლოგია

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დ. ფრანგიშვილი

აკადემიის უცხოელი წევრი, პასტერის ინსტიტუტი, მიკრობიოლოგიის განყოფილება, დოქტორ რუს ქუჩა 25, 75015 პარიზი, საფრანგეთი

შეხედულებები ვირუსების ბუნებასა და ევოლუციაზე იცვლება ბოლო წლებში, გარემოსთან დაკავშირებული ვირუსოლოგიის განვითარებისა და მიკრობების ვირუსების ახალი ჯგუფების დახასიათების შედეგად. ვირუსების ერთი საინტერესო ახალი ჯგუფის მასპინძლები ცოცხალი სამყაროს მესამე დომენს, არქეას, განეკუთვნებიან და ჰიპერთერმოფილებს წარმოადგენენ. ჩვენს მიერ ასეთი მასპინძლების ოცდაორი სხვადასხვა ვირუსი იქნა გამოყოფილი ევროპის, აზიის და ჩრდილო ამერიკის გეოთერმული წყაროებიდან. ამ ვირუსებს უნიკალური მორფოლოგიური და გენომური თვისებები აქვთ, განსხვავებული ბაქტერიებისა და ეუკარიოტების ვირუსებისგან. აქ მე მოკლედ ვაჯამებ ჩვენ შედეგებს და ვმსჯელობ მათ ზეგავლენაზე ვირუსების ბუნების, წარმოშობისა და ევოლუციის შესახებ არსებულ წარმოდგენებზე. ამ მსჯელობის შედეგად ვირუსი განისაზღვრება როგორც ორგანიზმი, რომელიც ლატენტურ ფაზაში არსებობს ვირიონისა და პროვირუსის სახით, პროდუქტიულ ფაზაში კი ვირიონების ფაბრიკის სახით. გარდა ამისა, მე ვანვითარებ შეხედულებას, რომ უჯრედებისა და ვირუსების წინამორბედები ერთდროულად წარმოიშვნენ სიცოცხლის ანცესტრალური ფორმებიდან და რომ ვირუსების ცხოვრების წესი, მათი გენომებისა და გენეტიკური ციკლების მრავალფეროვნება უჯრედების და ვირუსების წინამორბედების კო-ევოლუციის სხვადასხვა ეტაპების მატიანეა.

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