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REVIEW

Viruses Defined by the Position of the Virosphere within the Replicator Space

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SUMMARY Originally, viruses were defined as miniscule infectious agents that passed through filters that retain even the smallest cells. Subsequently, viruses were considered obligate intracellular parasites whose reproduction depends on their cellular hosts for energy supply and molecular building blocks. However, these features are insufficient to unambiguously define viruses as they are broadly understood today. We outline possible approaches to define viruses and explore the boundaries of the virosphere within the virtual space of replicators and the relationships between viruses and other types of replicators. Regardless of how, exactly, viruses are defined, viruses clearly have

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evolved on many occasions from nonviral replicators, such as plasmids, by recruiting host proteins to become virion components. Conversely, other types of replicators have repeatedly evolved from viruses. Thus, the virosphere is a dynamic entity with extensive evolutionary traffic across its boundaries. We argue that the virosphere proper, here termed orthovirosphere, consists of a distinct variety of replicators that encode structural proteins encasing the replicators' genomes, thereby providing protection and facilitating transmission among hosts. Numerous and diverse replicators, such as virus-derived but capsidless RNA and DNA elements, or defective viruses occupy the zone surrounding the orthovirosphere in the virtual replicator space. We define this zone as the perivirosphere. Although intense debates on the nature of certain replicators that adorn the internal and external boundaries of the virosphere will likely continue, we present an operational definition of virus that recently has been accepted by the International Committee on Taxonomy of Viruses.

KEYWORDS MGE, mobile genetic element, orthovirosphere, perivirosphere, replicator, virosphere, virus, virus classification, virus definition, virus taxonomy

INTRODUCTION

Organisms, which we here equate with cellular life forms, consist of one or numerous cells that reproduce via binary fission. With a few readily explicable exceptions, organisms (also known as reproducers) are subject to the incessant onslaught of diverse symbiotic (commensal, mutualistic, or parasitic) nonorganismal mobile genetic elements (MGEs), which are semiautonomous replicators (1–6).

The history of life is one of coevolution of organisms and MGEs. Indeed, theoretical models and computer simulations show that the emergence of parasitic or commensal MGEs is an intrinsic inalienable part of the evolution of all organisms (7–10). MGEs are ubiquitous in the biosphere. Packaged MGEs, also known as "virus particles (virions)," appear to be among the most common biological entities on earth, with many more virus particles than cells detectable in at least some environments (11–13)—although the distribution of the virus/cell ratios in different habitats varies substantially and remains a matter of ongoing investigation (14, 15). Along similar lines, typical genes of MGEs, such as those encoding transposases, are the most abundant genetic moieties in the oceans (16), and MGEs in different stages of decay account for most of the genetic material in many complex organisms with large genomes, such as animals, plants, and some protists (17, 18). Furthermore, MGEs are astonishingly diverse genetically and apparently comprise the largest gene pool in the biosphere (13, 19, 20). Some MGEs (e.g., viruses) play major roles in biogeochemistry by releasing into the environment vast amounts of carbon, nitrogen, and phosphorus from lysed host cells (13, 21–24). Finally, numerous viruses and even smaller virus-like agents, such as viroids and virusoids, are pathogens that cause diverse and, in many cases, devastating diseases in humans, livestock, or plants.

Like organisms, MGEs have their own genomes. However, in sharp contrast to organismal genomes, which all consist of double-stranded (ds)DNA, MGE genomes are represented by all known types of nucleic acids: single-stranded (ss)RNA, dsRNA, ssDNA, dsDNA, and DNA-RNA hybrids (25–27). Accordingly, the routes of MGE genome replication and expression substantially differ from the uniform DNA-RNA-protein scheme used by organisms (Fig. 1). This diversity of replication and expression strategies suggests the intriguing possibility that particular MGEs, in at least some aspects of their biology, recapitulate the primordial RNA world and the transition from that early stage of life's evolution to the modern era of DNA-based cellular life. The ubiquity of MGEs and their major role in the global ecology make it obvious that no adequate understanding—and no theory—of the functioning and evolution of the biosphere is possible without including MGEs as an integral key part.

Viruses are widely recognized as a distinct type of MGE, but there is currently no explicit definition of virus, and the place of viruses in the multidimensional parameter space of replicators (28, 29) has not been precisely defined. In this article, we explore

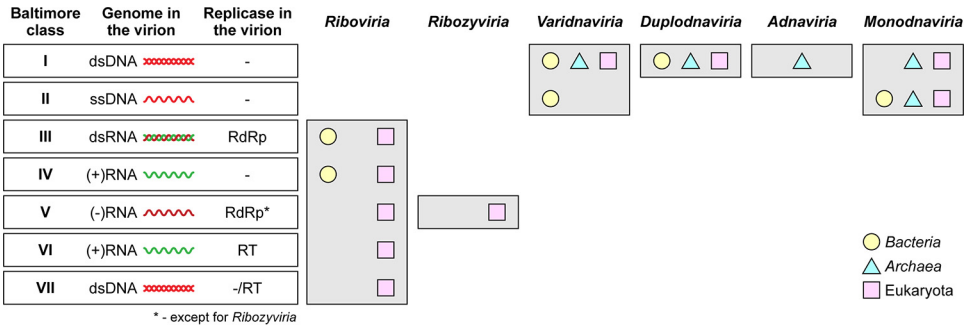

FIG 1 Viruses, their cycles of replication and expression, and the six monophyletic realms. The Baltimore classes (I to VII) (25) are shown in open boxes along with the major attributes characteristic for each class. Gray boxes, corresponding to each of the six monophyletic realms, are aligned with the Baltimore classes with which the member viruses are affiliated based on the type of nucleic acid encapsidated into their virions. The host range of viruses in each realm is indicated with different shapes: circles for bacteria, triangles for archaea, and squares for eukaryotes. RdRp, RNA-directed RNA polymerase; RT, reverse transcriptase.

different concepts and approaches to define viruses and differentiate them from other types of replicators. As we will outline, the issue is complex and multifaceted. Therefore, we approach it iteratively. First, we summarize the history of the term "virus" and some of the definitions that have been brought forward. Second, we identify the limitations of each of these definitions and narrow down the placement of viruses in the virtual replicator space. Third, we outline possible new definitions and the potential impact of these definitions on the virosphere composition as currently recognized by the International Committee on Taxonomy of Viruses (ICTV). In doing so, we explain which MGEs would have to be regarded viruses and which "viruses" would have to be reclassified as nonviral MGEs depending on each definition.

Genomes representing entire novel virus clades and large numbers of highly diverse other MGEs are being discovered at an incessantly accelerating pace, primarily through the advances of metagenomics (30, 31). Accurate analysis and classification of this growing volume of newly discovered MGEs urgently require refining our understanding of the overall structure of the replicator space.

VIRUS DEFINITIONS

Origins of the Term "Virus" (1398 to 1897 CE)

The word "virus" (from the Latin noun *virus*, which means "slimy liquid" or "poison") has been used since the late 14th century to refer to poisonous substances (32, 33). As early as 1728, the venereal disease-causing agents (today known as particular bacteria), and later, any infectious agents, indiscriminately were called "viruses" (32). In 1892, Ivanovskij demonstrated that the sap of a diseased tobacco plant remained infectious even after passage through Pasteur-Chamberland filters (pore size typically 0.2 μm) that were used to hold back cellular organisms, such as bacteria (34). Shortly thereafter, similar observations were made by Beijerinck, who also reported that filtered diluted tobacco plant sap remained as infectious as undiluted sap (35). Beijerinck referred to the agent in the filtered sap as a *contagium vivum fluidum* (a contagious living liquid). Subsequently, infectious agents that could pass through Pasteur-Chamberland filters were referred to as "ultra(filterable) viruses," and the agent causing tobacco mosaic disease was hence called tobacco mosaic virus (TMV) (36). With the increasing recognition that some agents specifically infected particular cellular organisms, the term "virus" was adopted exclusively for nonorganismal/noncellular filterable agents. Thus, "virus" was largely defined from then on through what it was not, i.e., viruses were considered noncellular, sub-light-microscopic infectious agents that could be separated from other infectious agents by filtration.

Early Clarity and Consensus Regarding the Term "Virus" (1898 to 1967 CE)

"TMV-like" entities that infect animals (foot-and-mouth disease virus), including humans (yellow fever virus), were discovered as early as 1897 to 1900 (37–39). The list

of viruses grew quickly, and early investigations indicated that all of these viruses shared certain properties: a particulate nature (40), substantial protein content (41), and defined morphologies in electron micrographs (42). Thus, by 1939, viruses were equated with virus particles, and these were conceptualized as infectious noncellular agents that depend on cells for their multiplication. The chemical, physical, serologic, and morphologic characterization of virus particles and their host tropism and effects on the hosts enabled the establishment of first virus classifications schemes (43–55). In a landmark paper published in 1957, Lwoff distilled the knowledge accumulated through the first half of the 20th century to formulate a biological definition of "viruses" as "strictly intracellular and potentially pathogenic entities with an infectious phase, and (i) possessing only one type of nucleic acid (DNA or RNA), (ii) multiplying in the form of their genetic material, (iii) unable to grow and to undergo binary fission, (iv) devoid of a Lipmann system (an active metabolism)" (56).

Erosion of the Virus Definition (1967 CE to Present)

In 1967, Diener and Raymer identified the cause of potato spindle tuber disease as a "virus with properties of a free nucleic acid," i.e., a nucleic acid not packaged in protein and not producing virions (57). Further characterization indicated that this free nucleic acid was too short to encode the proteins required for replication (58) (or, in fact, any proteins at all). Although this type of pathogen clearly was nonorganismal, ultrafilterable, and adhered to the Lwoff definition of "virus," Diener recognized the agent to be fundamentally different from the other thereto-described "viruses" and introduced the term "viroid" for distinction. The introduction of the concept of "viroid" marked the gradual realization of the plethora of MGEs known today, all of which could be considered "viruses" using the traditional virus definitions but were increasingly considered distinct from (now undefined) bona fide viruses. Such "virus-like" MGEs include virusoids (i.e., viroids that hijack the capsids of bona fide viruses for horizontal spread between hosts), satellite viruses (i.e., MGEs encoding one or more proteins required for virion formation but dependent on helper viruses for genome replication), and satellite nucleic acids (i.e., MGEs encoding replication factors but dependent on viruses for transmission that is achieved through encapsidation of the satellite nucleic acid into the capsids of coinfecting helper viruses).

Several other realizations and discoveries further eroded previous virus definitions. One striking case in point is the discovery and characterization of giant viruses, which, in their genomic complexity and virion sizes that match or surpass the smallest cellular organisms, encode a variety of typical cellular proteins (e.g., multiple translation system components) and are retained by Pasteur-Chamberland filters (59–61). In the wake of these discoveries, interest was rekindled to define viruses in a more comprehensive manner, striving to move away from simple but apparently inadequate traits, such as small size and infectivity. New definitions strived to capture essential features of genome content and reproduction that differentiate viruses from cellular life forms on the one hand and nonviral MGEs on the other hand. Thus, Raoult and Forterre defined viruses as "capsid-encoding organisms," in contrast to cellular life forms, which they defined as "ribosome-encoding organisms" (62). Subsequently, Claverie and Abergel defined a virus as any biological entity with a genome that is "replicated by a system of macromolecules that it does not entirely encode" and that is "disseminated using a metabolically inert structure, the maintenance of which does not require energy" (63). In a more recent elaboration, these authors further argued against the use of any virus definition based on the presence or absence of any subset of genes or physical features and concluded that viruses may be better defined by their generic properties of genome dissemination and propagation (64).

KEY ATTRIBUTES OF VIRUSES AND THEIR INADEQUACY FOR A VIRUS DEFINITION

Infectivity

Infectivity is, obviously, a hallmark of virus infections and hence was included in many previous virus definitions. However, counterexamples abound. With only a few

known exceptions, fungal viruses (generally referred to as "mycoviruses") are not infectious and instead are transmitted vertically or through hypha fusion during anastomosis between compatible mating types (65, 66). A similar lifestyle is adopted by numerous plant viruses (e.g., partitivirids) that cause persistent asymptomatic infections, lack an extracellular stage, and are only transmitted vertically (67, 68). Numerous "endogenous viruses," i.e., sequences derived from viruses and incorporated into organismal genomes (in particular, genomes of animals, including humans, as well as those of plants) (69, 70), serve as examples of viruses that are not infectious, as are the MGEs previously known as "polydnavirids" (71, 72) (in 2021 recognized as "polydnaviriformids" [73]).

Parasitism

Early on, viruses were recognized as obligate intracellular parasites, as in the famous quip of Peter and Jean Medawar: "A virus is a piece of bad news wrapped in protein" (74). However, crucial as it is, this intracellular parasitism cannot be the basis of a working definition of viruses. Although all viruses indeed reproduce solely within host cells, the reverse is false: numerous obligate intracellular parasites are bacteria or unicellular eukaryotes rather than viruses. Furthermore, not all (and possibly not even the majority of) viruses are detrimental to their hosts, and some appear to be outright beneficial, thus qualifying as commensals or mutualists rather than parasites (75–77), although the strict dependence on the host cell and intracellular reproduction remain universal traits of these replicators (78, 79).

Size

The original virus definitions were construed around the idea that viruses have a particulate nature (viruses = virus particles/virions) with distinct morphologies that can be visualized only by electron microscopy because of their small sizes. However, virions are only a part of the virus life cycle (80), conceptually similar to spores of bacteria or fungi (81). This idea has been further developed by Forterre, who proposed the virocell concept, according to which the infected cell, the virocell, is the "living form" of the virus (82–84). Logically, virus and virion therefore cannot and should not be equated (and, importantly, mature virions are primarily extracellular entities and hence would further confound the view of viruses being "obligate intracellular parasites" further). The distinction between "virus" and "virion" has important consequences for virus definitions: the morphological characterization of virions is not the same as characterization of the viruses that produce these virions, and consequently, viruses cannot be considered "small," although virions can be small indeed. Moreover, not all virions are small in the traditional ("ultrafilterable") sense. The discovery of giant viruses that infect unicellular eukaryotes shattered the demarcation between organisms and viruses by size, because the virions of giant viruses are larger than the smallest bacterial, archaeal, or picoeukaryotic cells. In fact, they are visible by light microscopy and do not pass Pasteur-Chamberland filters (59–61, 85). For instance, "pandoraviruses" have dsDNA genomes in excess of 2 Mbp in length and produce particles that are 1 μm in length (86, 87). Thus, for reasons both conceptual and practical, virion size cannot be a defining criterion for viruses. The alternative—classifying giant viruses as entities distinct from both viruses and cells ("giruses" [88] or "things resisting uncompleted classifications [TRUCs]" [89, 90])—appears to be untenable, given the demonstrable origin of giant viruses from smaller conventional ones (60).

Virions versus Ribosomes and Replication Machinery

The dissemination of replicators between susceptible hosts using protective shells, virions, is a property that could be exploited to distinguish viruses from other types of replicators. The simplest virions consist of a nucleic acid surrounded by a protein capsid that can be formed from one or several virus-encoded proteins and typically has icosahedral or helical symmetry (the terms virion and capsid are attributed to Lwoff et al. [91, 92]). In more complex virions, the nucleic acid-encompassing capsid can be further surrounded by one or more additional proteins and/or a lipid layer. In such cases,

the innermost layer of the virion surrounding the viral genome is usually referred to as the nucleocapsid (a term coined by Caspar and Klug [93]). Notably, nucleocapsid proteins of certain viruses that produce enveloped particles are homologous to the capsid proteins (CPs) of viruses producing nonenveloped particles, indicating that there is no major functional distinction between the two types of virion proteins (94).

Raoult and Forterre posited that viruses are capsid-encoding (and subsequently refined to virion-encoding [95]) organisms as opposed to cellular life forms that they defined as ribosome-encoding organisms (62, 84). This definition would include numerous MGEs that are currently considered viruses and exclude viroids *sensu stricto*. However, agents currently recognized by the ICTV in the established riboviriad families *Endornaviridae*, *Deltaflexiviridae*, *Hypoviridae*, *Mitoviridae*, and *Narnaviridae* and genus *Umbravirus*, which are common intracellular parasites of fungi, plants, and some unicellular eukaryotes, would not be viruses according to this definition: the genomes of most of these agents are never encapsidated, whereas, for instance, umbraviruses highjack capsids of other viruses for their dissemination. Thus, many MGEs are clearly evolutionarily related to bona fide viruses and resemble them in biological properties but do not encode capsids. An adoption of the Raoult-Forterre definition in its current form would necessitate the expulsion of the capsidless virus-like MGEs from the midst of viruses.

Conversely, bacterial gene transfer agents (GTAs) are virion-like particles that consist of homologs of proteins encoded by MGEs currently considered viruses by the ICTV (tailed bacteriophages of the duplodnaviriad phylum *Uroviricota*) but encoded by genes embedded in bacterial chromosomes, often in several blocks, rather than a single genomic segment (96–100). GTAs do not package the genes encoding the structural proteins of the virion-like particles but rather encapsidate random pieces of the host bacterial genome. GTAs are produced under stress, lyse the host cell, and "infect" neighboring cells, thus enhancing horizontal gene transfer. The genes encoding GTA components do not constitute proviruses: they have been fully domesticated and dispersed over the bacterial chromosome, and the genes responsible for the genome replication of the ancestral virus have been lost. Thus, essentially, the GTAs are virion-like entities encoded by bacteria and are not distinct replicators. Following Lwoff's definition as well as the Raoult-Forterre definition of viruses, GTAs should be considered viruses despite the absence of "viral" genomes. However, domestication fully transformed GTAs into functional cellular systems, and nobody refers to them as viruses in the literature, indicating that there is wide consensus that they are not viruses. The ICTV will likely consider them analogs of "polydnaviriformids," i.e., viriforms, rather than viruses if classification is attempted (73).

Finally, it remains to be seen whether ribosomes are hallmark properties of cellular organisms that are absent from MGEs in general and viruses in particular. At this time, we are unaware of any MGEs encoding functional ribosomes. However, "tupanviruses" and some "klosneuviruses" (tentative members or close relatives of the varidnaviriad family *Mimiviridae*) encode nearly complete translation systems, with the exception of the ribosome itself (85, 101, 102), and many prokaryotic viruses encode ribosomal proteins (103). Although no MGEs encoding ribosomal RNAs are currently known, it is difficult to confidently discard the possibility of discovering some MGEs that encode a complete ribosome. Thus, the criteria underlying the (seemingly) intuitive and sensible capsid-based definition of viruses—and their demarcation from ribosome-encoding cellular organisms—are far from being ironclad.

Claverie and Abergel's second criterion for their virus definition ("disseminated using a metabolically inert structure, the maintenance of which does not require energy" [63]) is also problematic, because many MGEs currently considered viruses by the ICTV, for example, some of the aforementioned "mycoviruses," do not produce virions. Moreover, the replication criterion fails as well, much like the ribosome criterion. Many large DNA viruses include most if not all of the key replication enzymes (104, 105), and the existence of MGE-encoded autonomous virus DNA replication machinery

appears quite likely. Even more obvious, the replication of RNA virus genomes is supported mostly by virus-encoded proteins. Furthermore, various MGEs typically not considered viruses, such as plasmids and transposons, are transferred between cells of organisms in all three domains of life within extracellular vesicles (106–111), which fit the definition of the virus particles proposed by Claverie and Abergel (63).

Thus, although the approaches based on the presence of virions and the absence of suites of proteins involved in quintessential cellular functions reflect major distinctive features of viruses, they fail to produce an all-encompassing definition of virus.

Absence of Metabolism

The absence of active metabolism has been a crucial feature of virus definitions since Lwoff first formulated his in 1957 (56). Indeed, most MGEs currently classified as viruses do not encode any components of ATP-generating metabolic systems. However, giant viruses, such as the recently described mimivirid Prymnesium kappa virus RF01, encode enzymes of the tricarboxylic acid (also known as Krebs) cycle and the β-oxidation pathway (112), whereas "pandoraviruses" (tentative members or close relatives of the varidnaviriad family *Phycodnaviridae*) not only encode enzymes of the tricarboxylic acid cycle but also produce particles capable of maintaining a proton gradient across the particles' membranes (113).

Along similar lines, many viruses infecting cyanobacteria ("cyanophages") encompass genes for all the components of photosystems that they often transfer between hosts, enhancing their photosynthetic capabilities (114, 115). Finally, virome analyses suggest that some viruses encode a set of proteins involved in oxidative phosphorylation, specifically, components of the prokaryotic electron transport chain complexes I, II, III, and IV, and even some subunits of the F_oF_1 ATP synthase, also referred to as complex V (116). Thus, the absence of metabolism cannot pass as a virus definition criterion, at least, unless the requirements for virus-encoded metabolic networks are carefully specified.

BOUNDARIES OF THE VIROSPHERE IN THE VIRTUAL SPACE OF REPLICATORS

Self-propagating biological entities are fundamentally split between reproducers (cells and such eukaryotic organelles as mitochondria and chloroplasts) that reproduce by various forms of division, retaining the physical continuity of their macromolecular organization, and replicators (all varieties of MGEs) for which replication of the genome alone is typically sufficient (5, 7, 117–119). All replicators depend on reproducers (cellular organisms) for energy and most molecular building blocks, and hence they are either parasites (if they decrease the fitness of the hosts), commensals (if host fitness remains unaffected), or mutualists (if they provide benefits to the hosts). The genomes of cellular organisms can be considered the ultimate mutualist replicators (29). Replicators share one universal property: they all possess some genomic elements that provide a degree of control over their own replication and thus make them distinct units of evolution. The complexity of such replication-controlling elements varies greatly from encoding effectively complete replication machineries (as in many large and giant DNA viruses and nearly all RNA viruses) to having only small structural elements recognized by host polymerases (e.g., viroids), but each replicator carries at least a minimal replication signal.

The discussion in the previous section should suffice to demonstrate that simple definitions of virus do not work, as there are too many exceptions for any obvious demarcation criteria. If we are interested in a meaningful answer to the question "what is a virus," a different approach is needed, and this is what we attempt here. We examine a multidimensional conceptual space of replicators. The dimensions of this space include genome length, genetic complexity, replicative autonomy, "selfishness," existence of an inert extracellular phase, and presence or absence of encoded particular functional systems (28). Using these dimensions, we attempt to delineate the subspace of the replicator space occupied by viruses: the virosphere. The core of the virosphere, which we define as the orthovirosphere, fits within virion-based virus definitions, but the boundaries are intrinsically blurry. We therefore also define a perivirosphere, i.e., a

subspace of the virosphere surrounding the orthovirosphere, including replicators that share some but not other characteristic features of "typical" viruses.

The Virosphere

Orthovirosphere and its boundaries. As commonly understood by most virologists in the absence of in-depth discussion, viruses are replicators but occupy a special place in the virtual replicator space. To define the boundaries of the virosphere and explore its blurry borders and passages to other parts of the replicator space, while not upending the virology community's overall understanding of virus, for purely historical reasons, we start with TMV, declaring it the "quintessential virus" (36, 120).

TMV has a short (~6 kb) linear positive-sense RNA genome that encodes only four proteins: a protein containing capping enzyme and RNA helicase domains, an extended version of this protein that additionally contains an RNA-directed RNA polymerase (RdRp) domain, a CP, and a movement protein (MP) that enables virus transmission among plant cells (36). After a TMV particle enters a host cell, the virus hijacks the host translation and endomembrane systems to produce virus proteins and replicates, resulting in the assembly of rod-like helical particles encapsidating progeny genomes. Small and simple as it is, TMV encompasses the two functional modules that characterize most viruses and, as such, can be expected to become an important ingredient of any virus definition: (i) replication and (ii) structure and morphogenesis. In addition, TMV possesses a third module, in this case, consisting of a single gene that is dedicated to virus-host interaction. Such an ancillary module is present in many but not all viruses, and more complex viruses can be considered to encompass multiple modules consisting of genes involved in interactions with different functional systems of the host, such as evasion of the host defenses. Apart from this canonical genetic-functional layout, TMV is endowed with biological capacities that are traditionally associated with viruses: TMV is a pathogen that causes acute infection and disease in its host and is readily transmissible among individual host organisms. Thus, in the virtual space bounded by various molecular and biological traits of replicators, we place TMV in the center of the virosphere (Fig. 2).

Starting from this "baseline" simple (albeit not the simplest) but functionally complete virus, we can explore different directions in the virosphere, aiming to track its boundaries. "Nothing in biology makes sense except in light of evolution" (121), and the virosphere is no exception. Trying to define the virosphere without understanding the routes of virus evolution would be futile. In this section, we trace the trajectories through which replicators enter and leave the virosphere (evolve to become viruses per our definition or evolve from viruses to other replicators) and, in many cases, the means by which they are getting stuck near its boundaries. In this virtual tour of the virosphere and the regions of the replicator space that surround it, we begin with the recently established megataxonomy of viruses, with its six top-ranked taxa, the realms (27, 122, 123):

1. *Riboviria*—RNA viruses (kingdom *Orthornavirae*) and reverse-transcribing viruses (kingdom *Pararnavirae*);
2. *Monodnaviria*—DNA viruses encoding HUH superfamily replication initiation endonucleases (but also including dsDNA viruses with small genomes, polyoma- and papillomavirids, in which this endonuclease is inactivated);
3. *Varidnaviria*—an enormous diversity of dsDNA viruses that produce particles with icosahedral capsids formed by double jelly roll (DJR) major capsid proteins (MCPs);
4. *Duplodnaviria*—the second realm of dsDNA viruses that includes viruses producing particles with icosahedral capsids built of so called HK97-fold MCPs (caudoviricetes of prokaryotes and animal-infecting herpesvirals);
5. *Adnaviria*—a new realm of archaeal viruses with dsDNA genomes and helical (nucleo)capsids built of unique alpha helical MCPs that dehydrate the viral genomes and transform them into A-form DNAs;

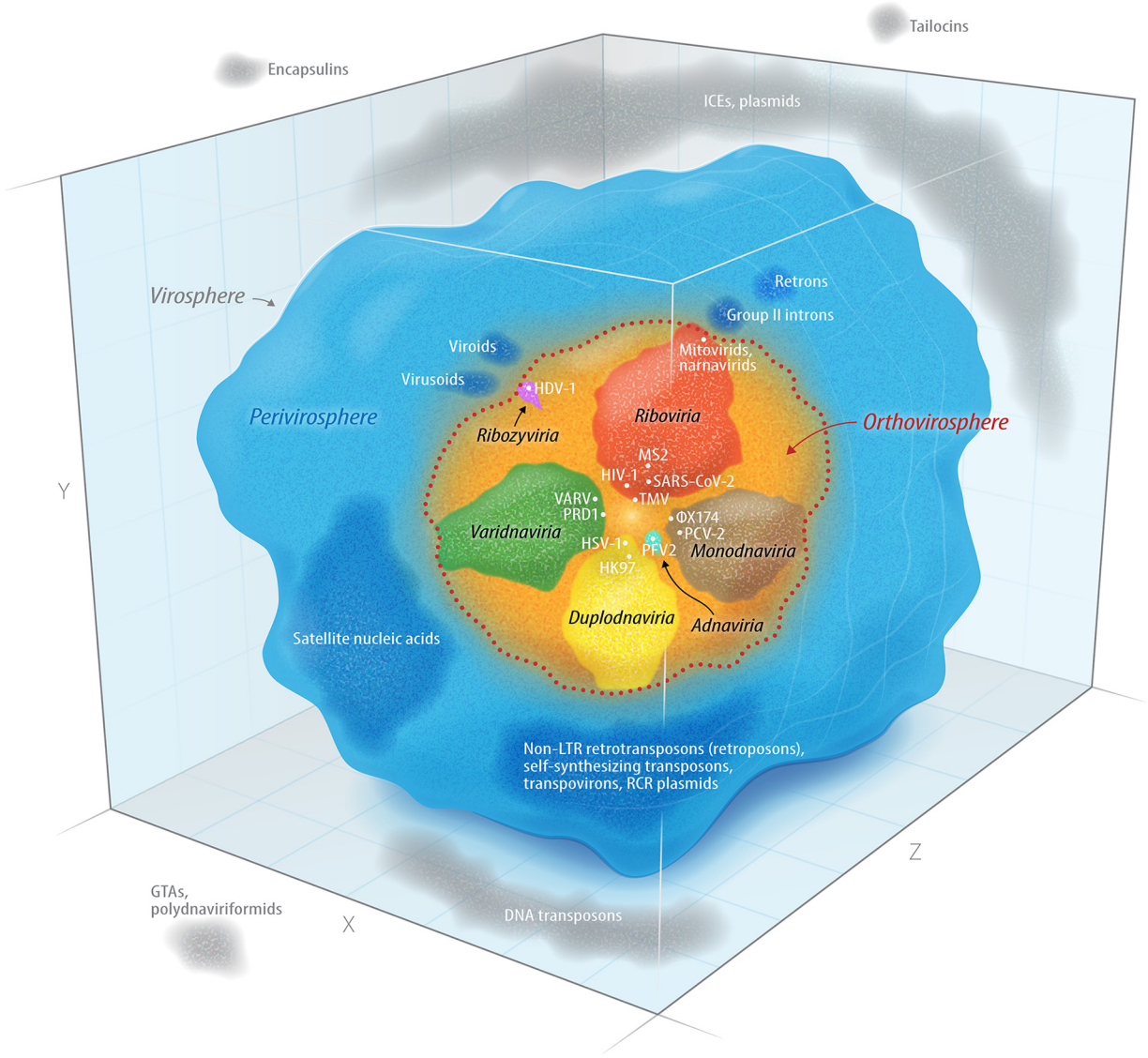

FIG 2 The virosphere—orthovirosphere and perivirosphere—within the replicator space. Tobacco mosaic virus (TMV) was the first replicating noncellular mobile genetic element (MGE) to be called "virus" and hence occupies the center of the debate of how viruses should be defined. Shortly after the discovery of TMV, other MGEs, such as enterobacteria phage PRD1, "phage lambda," and phage ΦX174, were discovered that, in some aspects, are fundamentally different from TMV but yet were quickly accepted as "viruses" by the scientific community. Hence, they are located close to TMV as "quintessential" viruses although they are phylogenetically unrelated. Today, these viruses are members of distinct, polyphyletic viral realms, with each relative of the quintessential viruses sharing, losing, or gaining certain properties that shape the debate on what constitutes a "virus." In the three-dimensional space of the virosphere, i.e., the space that is occupied by all MGEs, a fuzzy (red dotted) line can be drawn at arbitrary places that separate the orthovirosphere (bona fide viruses as per any established definition; orange) from the perivirosphere (virus-like MGEs; blue). The placement of the fuzzy line is determined by the scientific community's consensus about the nature of a particular MGE. For instance, there is no controversy about herpes simplex virus 1 (HSV-1) being a "virus," and there is little controversy about viroids and virusoids not being viruses. The line is fuzzy because MGEs exist that have or lack properties that make their placement challenging. For instance, hepatitis delta virus 1 (HDV-1), accepted as a "virus" by many (123), shares many properties with viroids and virusoids and hence is considered not to be a "virus" by others. GTA, gene transfer agent; HIV-1, human immunodeficiency virus 1; HK97, Escherichia coli phage HK97; ICE, integrative and conjugative element; LTR, long-terminal repeat; MS2, Escherichia coli phage MS2; PCV-2, porcine circovirus 2; PFV2, Pyrobaculum filamentous virus 2; RCR, rolling-circle-replicating; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; VARV, variola virus. For simplicity, organismal and organellar genomes have been omitted from the cubical extravirospherical replicator space.

6. *Ribozyviria*—circular, negative-sense RNA viruses related to hepatitis delta virus 1 (HDV-1) and other deltaviruses that share some key features with viroids but encode a virion protein.

We then briefly visit classified viruses that do not fit into any of the established realms and finish the discussion with an overview of nonvirus MGEs that are currently

classified by the ICTV (satellite DNAs, viroids, and viriforms) and unclassified MGEs (other satellite nucleic acids, virusoids, various transposons, and plasmids).

(i) *Riboviria*. *(a) Orthornavirae.* Numerous and highly diverse RNA viruses in the realm *Riboviria*, in principle, resemble TMV in both their genomic layout and biological properties. They encompass the two typical modules of virus genes, and many also possess a dedicated host-interaction module. In the now infamous coronavirids (124) and in flavivirids (125) and plant closterovirids (126) (the three groups of RNA replicators with the longest, most complex genomes), this module is notably expanded. On the other extreme of the RNA domain of the orthovirosphere are several groups of RNA replicators with extremely short genomes. An example is *Totiviridae*, a family of widespread dsRNA viruses with genomes of ~4 kb that are found in fungi, diverse protists, and invertebrate holobionts (65, 127). Totivirids only encode RdRp and CP, that is, minimal versions of the replication and structural modules, and are not infectious, i.e., they are transmitted only vertically. These replicators fit the virion-centric definitions of "virus" but, considering their biological properties, such as the lack of infectivity, would map to the periphery of the orthovirosphere (Fig. 2). It should be noted, however, that the simplicity of the genome layout and lack of infectivity are not tightly linked, as members of *Nodaviridae* that also have only two genes are typically fully infectious (128). Within our conceptual framework, such viruses belong closer to the center of the orthovirosphere than totivirids.

Consider "satellite viruses" that are associated with many plant RNA viruses. Satellite tobacco necrosis virus (STNV; unassigned riboviriad genus *Albetovirus*) can be seen as the archetype of satellite viruses. STNV has a short (~1.2 kb) RNA genome that only encodes a CP and hijacks the RdRp of its helper virus, tobacco necrosis virus (*Tombusviridae*: *Alphanecrovirus*), for replication (129, 130). It makes sense to classify STNV and other similar agents as bona fide viruses because they are distinct CP-encoding replicators (129). However, these viruses lack genes encoding RdRps, the only universal gene of RNA viruses, and thus the replication module. Consequently, they strictly depend on their helper viruses for replication and therefore belong at the periphery of the orthovirosphere.

Whereas satellite RNA viruses, such as STNV, retain the structural but not the replication module, numerous replicators with RNA genomes that are currently officially recognized as viruses by the ICTV have lost the structural module, retaining only the RdRp-encoding gene and, in some cases, genes encoding additional proteins involved in replication and/or interactions with their hosts. There are at least five distinct independently evolved groups of RNA replicators in this category that currently have official status as viruses:

i) *Deltaflexiviridae*: RNA elements that infect fungi and that are apparently derived from capsid-encoding viruses of the alsuviricete order *Tymovirales* (131);
ii) *Endornaviridae*: relatively large, complex RNA elements derived from plant alsuviricetes that encode a variety of proteins involved in replication and MGE-host interaction, but not CPs, and are widespread in plants, fungi, and oomycetes (132, 133);
iii) *Hypoviridae*: RNA elements that propagate in fungi and are likely derivatives of plant viruses assigned to stelpaviricete *Potyviridae* (134, 135);
iv) *Mitoviridae* and *Narnaviridae*: groups of minimal RNA elements that encode only RdRps, are derived from prokaryotic RNA viruses (*Leviviricetes* [136]) and replicate in mitochondria or the cytoplasms of plant, fungal, or unicellular eukaryotic cells (137);
v) *Umbravirus*: RNA MGEs that infect plants and that are evolutionary derivatives of tombusvirids. These MGEs encode an RdRp and two MPs, but they hijack CPs from helper viruses at some stages of their reproduction cycles (138).

Most of these naked RNA MGEs are harmless to their hosts and are transmitted only vertically, although some umbraviruses and hypovirids are pathogens.

There is little doubt that more capsidless RNA replicators will be discovered as the known diversity of RNA replicators expands, especially as these elements often lack

obvious biological manifestations and are only discovered by metatranscriptome analysis. All of these replicators are traditionally denoted viruses although they fail the virion-centered definitions. The strong justification for considering them in the same plane with bona fide viruses is the RdRp phylogeny, which shows beyond reasonable doubt that all of these elements evolved from viruses on multiple independent occasions via parallel routes, i.e., by losing the CP gene (139, 140). However, at least in cases in which these agents are not pathogenic, one could argue that they have morphed into a different kind of replicator that might be best defined as an RNA plasmid. There is no way of making an "objective" call on whether these MGEs are viruses. Rather, these elements formally belong in the perivirosphere by virtue of not encoding a CP, but being derivatives of bona fide viruses, they reside at the very boundary of the orthovirosphere.

(b) Pararnavirae. From RNA viruses that replicate without a DNA stage, we move to reverse-transcribing viruses that are related to orthornavirans by virtue of the homology of their replicative enzymes, the reverse transcriptase (RT) and RdRp, respectively. Evolutionary reconstructions clearly show that pararnavirans evolved from capsidless and thus, arguably, nonviral retroelements (141, 142). Such retroelements are common (even if dramatically different in abundance) in organisms of all major taxa. Reverse-transcribing viruses, on the other hand, are a eukaryotic innovation that was brought about by the capture of the CPs from unknown sources, apparently on two independent occasions, in the orders *Ortervirales* and *Blubervirales* (*Hepadnaviridae*) (142, 143).

In addition to the well-known retrovirids with RNA genomes and caulimovirids and hepadnavirids with DNA genomes, distinct reverse-transcribing viruses have been classified in families *Belpaoviridae*, *Metaviridae*, and *Pseudoviridae*. However, these three groups of viruses are more frequently referred to as Bel/Pao-like, Ty3/Gypsy-like, and Ty1/Copia-like long-terminal repeat (LTR) retrotransposons, respectively (144). Indeed, these elements spend most of their reproduction cycles as transposons integrated in the genomes of their hosts (diverse unicellular eukaryotes, fungi, plants, and animals). Nevertheless, they retain the genes for structural proteins and form intracellular virion-like particles, the role of which is not fully understood (145, 146). Notably, virions produced by metavirid Gypsy are infectious in the classical sense, i.e., extracellularly (147), indicating that at least some of these retroelements are bona fide viruses. However, most belpaovirids, metavirids, and pseudovirids appear to represent a departure from the core of the orthovirosphere toward the perivirosphere. It would be legitimate to denote these MGEs as "virus-like transposons," but "transposon-like viruses" seems equally fitting if not more accurate. By virtue of carrying genes for structural proteins and forming virions, these MGEs belong in the orthovirosphere but, clearly, on its periphery, given their transposon-like lifestyle. It should be noted, however, that the transmissible retrovirids, such as human immunodeficiency virus 1 (HIV-1), also encode integrases. In their life cycles, these viruses go through an obligatory stage of integration within their host genomes, where many remain dormant for extended periods of time (148) and can be domesticated and/or deteriorate eventually. Thus, many if not most reverse-transcribing viruses display a continuum of propagation modes, from virus to transposon.

(ii) *Monodnaviria*. The ssDNA MGEs classified in realm *Monodnaviria* are small typically circular replicators with a peculiar evolutionary history. These ssDNA viruses evolved from small bacterial or archaeal plasmids on multiple independent occasions via parallel routes. In both cases, viruses evolved via the capture of genes encoding CPs, from preexisting RNA viruses, or from yet unknown sources (149). The plasmids contributed the replication module, in this case, the HUH superfamily endonuclease involved in the initiation of rolling-circle replication (150). Thus, this is a clear-cut case of the origin of viruses from nonviral MGEs. Notably, on at least one occasion, the reverse course of evolution, i.e., emergence of a group of plasmids in *Phytoplasma* (plant-pathogenic) bacteria from ssDNA viruses of plants, occurred as well (150). Thus, these replicators that, in their current state, can be considered typical viruses have

entered (or left) the virosphere on multiple occasions. In addition to ssDNA viruses, the realm *Monodnaviria* includes two groups of dsDNA viruses (*Papillomaviridae* and *Polyomaviridae*) with short circular genomes, which encode an inactivated HUH endonuclease in accordance with their changed mode of replication (i.e., a switch from rolling-circle replication to the standard mechanism of dsDNA replication). These viruses are even further removed from the plasmid origins than their ssDNA virus ancestors.

Satellite nucleic acids of the family *Alphasatellitidae* represent another interesting assemblage of MGEs that are functionally and evolutionarily linked to eukaryotic ssDNA viruses, in this case, phylum *Cressdnaviricota* (151, 152). Alphasatellitids are short (~1 to 1.4 kb) circular ssDNA molecules transmitted within the capsids of plant viruses of the monodnaviriad families *Geminiviridae* and *Nanoviridae* (152, 153). They encode a single protein, the replication initiation endonuclease, which is phylogenetically closely related to that of nanovirids, and resemble the R-component of the multipartite nanovirid genome. Whereas the Rep protein encoded by the R-component of nanovirids is responsible for the replication of all genome components, the Rep protein of alphasatellitids exclusively replicates the cognate DNA molecule. By virtue of not encoding their own CPs, alphasatellitids clearly do not belong in the orthovirosphere but rather in the perivirosphere. However, alphasatellitids encode the hallmark Rep protein, which holds together the realm *Monodnaviria* and, more specifically, can be placed deeply within phylum *Cressdnaviricota* by phylogenetic analysis (151). Thus, there is no fundamental functional difference between alphasatellitids and capsidless RNA viruses, especially umbraviruses, which are also encapsidated into the capsids of other viruses. Furthermore, certain alphasatellitids have apparently forged symbiotic alliances with viruses, which arguably draws alphasatellitids away from the perivirosphere and back into the orthovirosphere. In particular, the genomic components encoding the CPs and the putative MP of coconut foliar decay virus (CFDV), the sole member of the newly established virus family *Metaxyviridae* (154), are replicated by the Rep encoded by one of the nine alphasatellitids associated with CFDV, rendering it an indispensable component of the CFDV genome (155).

(iii) *Varidnaviria*. In addition to legitimate dwellers of the orthovirosphere, such as tectivirid bacteriophages or vertebrate adenovirids, the replicators classified in realm *Varidnaviria* include the giant viruses mentioned in the beginning of this article, many of which are typical, albeit complex, viruses. However, some MGEs currently considered giant viruses, such as "pandoraviruses" and "pithoviruses" (tentative members of megaviricete order *Pimascovirales*), challenge historic virus definitions (61, 63, 156). Even to a greater extent than for the MGEs officially classified in *Mimiviridae* ("microbe-mimicking viruses"), the particles of "pandoraviruses," "pithoviruses," and "pithovirus"-related "cedratviruses" and "orpheoviruses" superficially resemble cells, in both size and shape (86, 87, 157–160). These viruses lack typical capsids and CP but do encode the structural components of their virions (86, 87). In the case of "pandoraviruses," one of the two major virion proteins evolved from a minor structural protein found in other giant viruses (161). Thus, these are bona fide viruses that remain within the orthovirosphere even if, along the size and complexity axes, they deviate far from the orthovirosphere core.

Similar to the reverse-transcribing pararnavirans that include numerous replicators that are traditionally considered transposons rather than viruses, dsDNA *Varidnaviria* includes a large assemblage of MGEs, known as polintons or mavericks, which encode retroviral-like integrases and are integrated within the genomes of diverse eukaryotes (162–164). Although originally described as a class of large DNA transposons, these elements were subsequently found to also encode a conserved morphogenetic module typical of varidnaviriads, including the DJR MCP, a single jelly roll (SJR) minor CP (mCP), an A32-family genome packaging ATPase, and a capsid maturation protease (165). Hence, it has been suggested that polintons are bona fide viruses, dubbed "polintoviruses." Although reactivation and formation of virions remains to be demonstrated for any "polintovirus," they have been hypothetically placed at the center of evolutionary events leading to the emergence of all eukaryotic members of *Varidnaviria* (166–168).

Furthermore, an expansive group of polinton-like viruses ("PLVs") has been identified by analysis of metagenomes from diverse environments (169, 170), and for at least one of the "PLVs," virions have been observed (171).

Given their predominantly transposon lifestyle (and until virions are characterized), "polintoviruses," despite their apparent key role in the evolution of *Varidnaviria*, may be perceived as peripheral members of the orthovirosphere. Moreover, some polinton-like transposons have lost the capsid protein genes, which pushes them into the perivirosphere. In contrast, the "PLVs" are closer to the center of the orthovirosphere. Transpovirons, a group of plasmid-like linear dsDNA MGEs that depend on giant viruses for replication (172, 173), also appear to derive from polintons, via a deeper degradation that involved not only the loss of the morphogenetic genes but also inactivation of the DNA polymerase (174). Thus, transpovirons are typical members of the perivirosphere.

In the course of varidnaviriad evolution, even more dramatic departures from the core of the virosphere have occurred. In particular, linear cytoplasmic plasmids found in fungi encode DNA polymerases that are closely related to those of "polintoviruses" as well as capping machineries and RNA polymerases shared with giant viruses, but they lack the morphogenetic module (166–168). These plasmids cannot be considered part of the orthovirosphere, being conceptually similar to the capsidless RNA viruses discussed above. Another group of linear plasmids, which has ventured even further away from the orthovirosphere, replicate in plant and fungal mitochondria and apparently evolved from bacterial tectivirids following the same evolutionary trajectory as narnavirids and mitovirids (168). All of these elements belong in the perivirosphere.

(iv) *Duplodnaviria*. Realm *Duplodnaviria* includes the enormously abundant and diverse tailed bacteriophages of class *Caudoviricetes* and related archaeal viruses, along with their eukaryotic relatives, the herpesvirals, which infect animals; all of these viruses are united by a highly conserved morphogenetic module. Numerous prokaryotic duplodnaviriads alternate between lytic and lysogenic cycles, with integrated proviruses vertically inherited across many host generations (175, 176). Some of these viruses, such as bacteriophage Mu and its close relatives, are also endowed with a transposition capacity (177, 178). Similarly, many herpesvirals persist in the host cells as episomes or as proviruses integrated in the host chromosome (79, 179, 180).

All of these replicators remain within the orthovirosphere but, from a functional standpoint, approach other domains of the replicator space. Remarkably, genomes of fish of several species contain giant (~180 kb) transposable MGEs called teratorns, which are hybrids of alloherpesvirids and piggyBac transposons (181). Teratorns proliferate within the host genomes as transposons, but the alloherpesvirid genome replication and morphogenesis modules also appear to be intact, suggesting that teratorns can lead dual life cycles akin to retroviruses and polintoviruses. GTAs, discussed in "Virions Versus Ribosomes and Replication Machinery," represent a case of an even more drastic derivational evolution of viruses whereby they are exapted for a cellular function (182). However, GTAs only propagate vertically within bacterial chromosomes. Thus, they are not replicators but, instead, are parts of the mutualist replicator, the prokaryote chromosome. Accordingly, notwithstanding their obvious virus ancestry and virus-like properties, GTAs are excluded from the replicator space altogether.

An even further departure from the virus state is represented by the tailocins (also known as type IX secretion systems), which are prokaryotic virion tails that were domesticated by bacteria and archaea on several independent occasions and function as secretion and delivery devices primarily for toxins (183–185). Tailocins are secreted with their cargo, adhere to target cells, and inject toxins in a manner that viruses would inject virus DNA in a standard infection. Tailocins are obviously virus-derived entities but, again, are not bona fide replicators and thus reside outside the replicator space.

(v) *Adnaviria*. Adnaviriads form filamentous helical virions which can be either enveloped or nonenveloped. All known members of this narrow realm, established in 2021 (122), are viruses that infect hyperthermophilic archaea (186). As in the case of varidnaviriads and duplodnaviriads, adnaviriads are held together by the shared

morphogenetic module. The virions are built from one or two paralogous α-helical MCPs, which have a unique fold (186–190). As a result of extensive interaction with the MCPs, the linear dsDNA genomes of adnaviriads change the conformation from the physiologically more common B form to the A form (hence the name of the realm) (191). Adnaviriads are bona fide viruses with lytic life cycles, but the replication modules are not identifiable from the genome sequences, suggesting that they rely primarily on the cellular replication machinery (192). No capsidless derivatives (or ancestors) of adnaviriads have been identified so far; thus, this realm does not appear to extend beyond the orthovirosphere.

(vi) *Ribozyviria*. This new realm of viruses, established in 2021 (123), currently includes a single family (*Kolmioviridae*) for HDV-1 and its close and more distant relatives (deltaviruses, "epsilonviruses," and "zetaviruses") recently identified in various vertebrates (193–199). HDV-1, which is highly virulent for humans, has a short (~1.7 kb) covalently closed circular (CCC) RNA genome that encodes a protein, delta antigen, which binds the HDV-1 genome, forming a nucleoprotein complex (200, 201). To attain infectivity, the nucleoprotein further hijacks the hepatitis B virus (HBV; *Hepadnaviridae*) envelope protein that determines HDV-1 tropism, but can also use envelope proteins of other helper viruses (202, 203). The HDV-1 RNA shares structural features with viroids (198, 204) and, like the latter, is replicated by host DNA-directed RNA polymerases via a rolling-circle mechanism (205, 206). Conceivably, HDV-1 and related ribozyviriads are evolutionary derivatives of viroid-like MGEs, although no homology with currently known viroids has been detected. The provenance of the nucleocapsid protein remains obscure. By virtue of encoding the nucleocapsid protein, forming virions, depending on bona fide viruses for their reproduction and causing disease, ribozyviriads are formally recognized as viruses (123). These viruses appear to represent a group of MGEs that have evolved to become viruses, thus mapping to the boundary between the orthovirosphere and perivirosphere.

Beyond the Blurry Boundaries of the Orthovirosphere: Highly Derived Denizens of the Perivirosphere

In the discussion of the established virus realms above, we have pointed out many groups of MGEs that are clearly derived from viruses proper but have lost the principal features of the virus state, in particular, genes for virion proteins, and thus should be relegated to the perivirosphere. Here, we discuss MGEs that differ from viruses even more dramatically yet possess some key virus-like features.

Viroids. Continuing down the scale of the complexity of ICTV-classified MGEs, there are viroids and satellite RNAs and DNAs, which the ICTV currently recognizes as nonviral or subviral MGEs (currently classified in families named with the suffixes *-viroidae* and *-satellitidae*, respectively).

Viroids are 220- to 450-nucleotide (nt)-long CCC RNAs that do not encode any proteins, are not encapsidated, and are replicated by host DNA-directed RNA polymerases or by RdRp of helper viruses through a rolling-circle mechanism (207, 208). The resulting genome concatemers are cleaved into monomers via self-splicing hammerhead ribozymes (*Avsunviroidae*) or by cellular enzymes (*Pospiviroidae*) (209, 210). These remarkable elements are minimal replicators and minimal infectious agents. Normally, viroids are not viewed as viruses, though they clearly possess virus-like properties, such as partial replication autonomy, filterability, infectivity, and, in some cases, pathogenicity. However, there is no evidence of a viral origin for viroids. We are left with the conclusion that viroids belong in the perivirosphere but, in several dimensions, map close to the boundaries of the orthovirosphere.

Satellite RNAs. Satellite RNAs, short (~400 nt) infectious RNA molecules that do not encode any proteins, are replicated by host DNA-directed RNA polymerases or by RdRps of helper viruses (211, 212). Like viroids, satellite RNAs are not viewed as viruses despite possessing virus-like properties, such as filterability, infectivity, and, in some cases, pathogenicity. Some satellite RNAs resemble viroids by being CCC RNAs, but they are encapsidated and transmitted within capsids of bona fide viruses. These are

sometimes referred to as "virusoids" and conceptually resemble ribozyviriads, with the major difference that virusoids do not encode any proteins, and in that respect, are analogous to viroids (213, 214). However, the short (220 nt) circular satellite of rice yellow mottle virus (scRYMV) is a typical virusoid in genomic structure (CCC RNA) in that it requires a helper virus (RYMV; *Solemoviridae*: *Sobemovirus*) for packaging, but its entire genome codes for a protein that is, however, not a CP (215). Conceptually, as long as encapsidation into a replicator-encoded capsid is considered a key component of a virus definition, virusoids, scRYMV, and other satellite RNAs are akin to viroids and also belong to the perivirosphere.

Satellite DNAs. Betasatellites and deltasatellites are two groups of satellite ssDNA molecules (in addition to alphasatellitids discussed above) associated with geminivirids and classified into two separate genera within the family *Tolecusatellitidae*. Unlike alphasatellitids, betasatellites and deltasatellites encode neither capsid (by definition) nor replication proteins, with deltasatellites being noncoding altogether (216–219).

Tolecusatellitids contain a hairpin loop that serves as the origin of the rolling-circle replication mediated by the Rep protein of the helper virus. No other similarity has been recognized between tolecusatellitids and viruses (220). Thus, although tolecusatellitids are bona fide replicators that exploit virus replication machinery and are encapsidated and transmitted by viruses, they are typical denizens of the perivirosphere.

From the Perivirosphere into the Open Replicator Space

The outer boundary of the perivirosphere, which is arguably even more blurry than the orthovirosphere boundary, faces the open replicator space (Fig. 2). Apart from the organismal genomes that, all together, represent a single type of mutualist replicator, the replicator space is occupied by a broad variety of MGEs, including diverse transposons, plasmids, and conjugative elements.

Non-LTR retrotransposons. In the phylogenetic tree of the RTs, *Pararnavirae* comprise a single strongly supported clade, whereas several other clades consist of various non-LTR retrotransposons (that is, those that lack long-terminal repeats characteristic of integrating reverse-transcribing viruses) and various domesticated RTs comprise several other clades (141, 221). Furthermore, non-LTR retrotransposons are ubiquitous in nature, whereas pararnavirans are strictly limited to eukaryotes. Therefore, there is no reasonable doubt that reverse-transcribing viruses evolved from non-LTR retroelements. However, the specific ancestors of pararnavirans are hard to identify. The top candidates seem to be group II self-splicing introns, which are highly conserved, widespread prokaryotic retrotransposons that are also integrated in organelle genomes and are thought to have played a key role in the evolution of eukaryotes, giving rise to spliceosome components and spliceosomal introns (222–224). Non-LTR retrotransposons are linked to riboviriads through the homologous RTs and, in terms of lifestyle, are similar to metavirids and pseudovirids, with the difference that the retrotransposons lack the genes for virion components and hence do not form virions. Although retrotransposons are neither infectious nor pathogenic, these virus-like features place them at the boundary of the perivirosphere.

DNA transposons. Most of the hugely diverse DNA transposons are not virus-like, either in evolutionary or in functional terms. However, several groups of transposons are connected to the virosphere. Polintons and Mu-like bacteriophages were already discussed above. Casposons—a group of prokaryotic transposons encoding an integrase homologous to Cas1, the adaptation integrase of CRISPR-Cas systems, and a DNA polymerase—resemble polintons by being self-synthesizing transposons (167, 225, 226). Notably, a small group of casposons integrated in the genomes of *Streptomyces* bacteria encode DJR-MCP and thus appear to represent integrated virus genomes (227). Thus, casposons are connected not only to the perivirosphere but also to the orthovirosphere.

Plasmids and Integrating Conjugative Elements

As is the case with transposons, most of the remarkable variety of known plasmids are not virus-like. However, there are multiple exceptions whereby not only the

evolutionary histories of viruses but also their infection cycles are intertwined with those of diverse plasmids. The origin of monodnaviriad replication modules from rolling-circle replicating plasmids is discussed above. In bacteria and archaea, many groups of plasmids act as satellite nucleic acids and hijack the virions of coinfecting viruses. Such hyperparasitism typically decreases the fitness of helper viruses. The classical P2-P4 system, in which P2 is the helper phage and P4 is the satellite plasmid that encodes one of the virion components, is the best-studied example (228–230). This system combines a typical virus with the P4 element that belongs in the perivirosphere.

Another well-studied case of satellite plasmids is presented by phage-inducible chromosomal islands (PICIs), first discovered and most extensively studied in *Staphylococcus aureus* bacteria (231, 232). PICIs are integrated in host chromosomes but are reactivated and excised during phage infection. They do not encode major virion components but hijack the virions of coinfecting viruses, often by modulating the specificity of the packaging machinery and inducing the formation of small capsids that can accommodate the PICI DNA but not the phage genome. PICI particles are released by phage-induced cell lysis and infect susceptible hosts, thus ensuring horizontal spread.

Along similar lines, some archaeal plasmids also hijack the virions of lemon-shaped viruses (233, 234). These satellite plasmids encode functional replication modules, typically unrelated to those of the helper viruses, and thus are distinct replicators and, by virtue of their functional link with viruses, belong on the boundary of, if not within, the perivirosphere. Furthermore, bacterial viruses often recombine with plasmids forming hybrid entities, sometimes denoted as phage-plasmids, which encompass genes of both plasmids and viruses (235), highlighting an extensive gene flow between these the two types of replicators. Extensive gene sharing between viruses and plasmids has also been observed in archaea (192, 236). These hybrid entities are notable manifestations of junctions between the outer replicator space and the virosphere.

Beyond the replicator spaces: nonreplicator virus derivatives. We have focused on the place of the virosphere in the replicator space. However, the virosphere protrudes out of the replicator space too, through derivatives of viruses that have lost their identity as replicators while retaining other virus-like features. We have already discussed GTAs and tailocins, remarkable virus-like entities that are not distinct replicators but rather domesticated parts of the organismal replicators (prokaryotic chromosomes). Here, we briefly touch upon several other cases of such exaptation of virus gene modules and individual genes that retain various degrees of the virus-like character.

"Polydnaviriformids." "Polydnaviriformids" are remarkable MGEs with a unique lifestyle. "*Polydnaviriformidae*" are a polyphyletic assemblage of MGEs derived from several different groups of large DNA viruses of insects (72, 237–239). The origin of the members of "*Bracoviriform*," one of the genera included in "*Polydnaviriformidae*," has been confidently traced to viruses classified in *Nudiviridae* (240), a group related to baculovirids, putative peripheral members of the realm *Varidnaviria*. "Polydnaviriformids" are mutualist symbionts of diverse parasitoid wasps whose genes are integrated in the wasp genomes but also form circular host-derived DNA segments packaged into virions. These virion-like particles, which do not encase "polydnaviriformid" genomes, are coinjected with wasp eggs into the insect prey and produce proteins that inhibit the prey's immune response and thus enable wasp development. Due to the lack of viral nucleic acids in the particles, entry of the particles into host cells does not establish infections. Examination of "polydnaviriformid" genomes reveals a mosaic of virus-derived and host-derived genes, with many of the former showing clear signs of deterioration. Thus, these elements are evolutionary derivatives of viruses that have departed the virosphere and the replicator space itself because they are technically not replicators. The close analogy between "polydnaviriformids" and GTAs is obvious (182, 241).

Encapuslins. Encapsulins are homologs of the CPs of ICTV-recognized *Caudoviricetes*. Encapsulins form capsid-like nanocompartments used for storage of various compounds by diverse bacteria and archaea (242, 243). Even if encapsulins evolved from virus genes (the direction of evolution, in this case, remains unclear), they are cellular proteins encoded

by vertically transmitted genes. In a close analogy, animals encode multiple domesticated homologs of retrovirus capsid (Gag) proteins, some of which form particles that apparently are involved in intercellular RNA transport (244–246). Thus, many cellular organisms encode capsids, although, to our current knowledge, these do not encapsidate the genes encoding the respective CPs. Therefore, although not being replicators, these entities have a link to the virosphere.

CONCLUDING REMARKS: VIROSPHERE AND REPLICATOR SPACE

Definitions are generally tricky outside mathematics and especially iffy in biology. Nevertheless, detailed examination of potential definitions of major categories of biological entities can be constructive, allowing one to get a grasp of the organization of the respective virtual biological spaces. There might not be much in a name as such, but understanding not only evolutionary but also structural and functional relationships between different types of biological entities is important.

The emergence of the virosphere was a very early event in the history of life, but one that occurred after the origin of diverse reproducers and replicators. The structural components of viruses are not monophyletic but, rather, were apparently acquired from cells on multiple independent occasions (247). Some of these acquisitions of virion components, in particular, exaptation of a carbohydrate-binding protein as the jelly roll CP, appear to have occurred very early in the evolution of life, long antedating the last universal cellular ancestor (LUCA) (248). Other groups of viruses probably emerged and acquired their virion proteins later in the course of life's evolution. Hence the key feature of the orthovirosphere and perivirosphere is that they are actively evolving regions of the replicator space that is highly dynamic as a whole, with the boundaries between and around them being inherently blurry zones rather than sharp lines. As demonstrated here by numerous examples, the evolutionary traffic into and out of the virosphere is an incessant process accompanying all evolution of life, in sharp contrast to the replicator-reproducer boundary that, to our current knowledge, has never been crossed during the evolution of life (Fig. 3).

The question "what is a virus" can be approached from two fundamentally different angles. One option is to develop a definition *ab initio* based on what would be found reasonable to consider a virus, see which known replicators fit this definition, name those replicators viruses, and exclude all others. We do not see this as a viable approach, because taking this road would likely upend the entire framework of virology, even if a consensus on such an *ab initio* definition could be achieved within the community.

The other option is the approach we take here: accept the long-held consensus that typical members of each of the virus realms (for example, TMV in the case of *Riboviria*) are indeed viruses. Accordingly, viruses can be defined starting from these indisputably viral replicators and then, moving gradually across the replicator space, examining at which point certain replicators should not qualify as viruses (Fig. 2). This approach led us to define the orthovirosphere and perivirosphere with blurry boundaries, which make a fully consistent and universal virus definition impossible. Nevertheless, an operational definition of viruses should be useful, even if only for pragmatic purposes, i.e., to delineate the set of replicators that should be classified by the virology community and separate them from those that should fall under the purview of other scientific communities. A virion-based definition captures a crucial feature of most MGEs currently considered viruses and can be adopted to define the orthovirosphere.

Defining viruses as "replicators that encode structural proteins encasing their own genomes" might be the closest one can get to a single-sentence definition.

All MGEs that are believed to have evolved from viruses but do not meet this definition, such as the numerous capsidless RNA "viruses" as well as virus-derived plasmids, belong to the perivirosphere. Minimal replicators, such as satellite nucleic acids and viroids, the propagation of which often depends on viruses and which can be encapsidated into the capsids of bona fide viruses, belong to the perivirosphere as well. In contrast, diverse virus derivatives that do not encapsidate their own genomes and

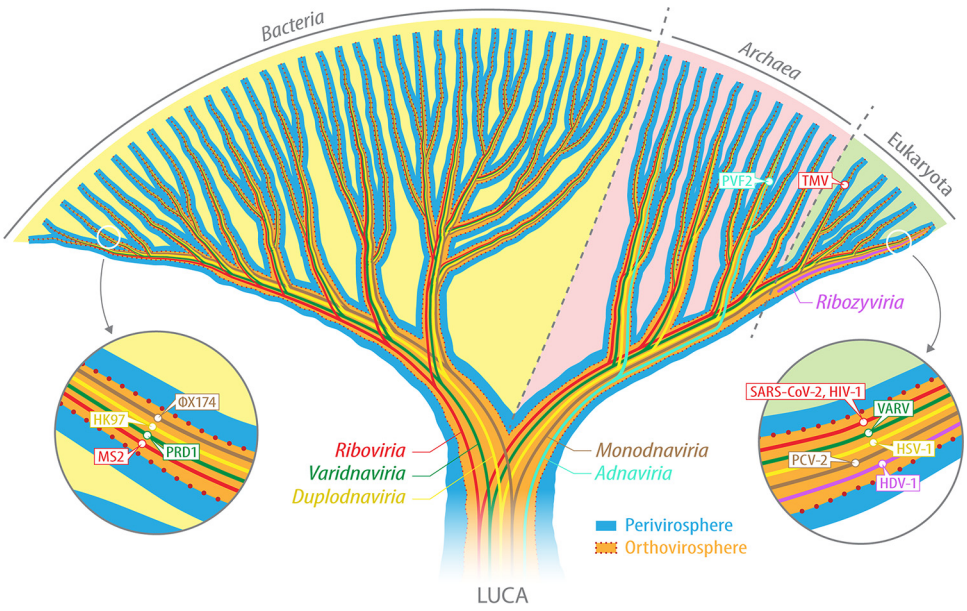

FIG 3 Evolutionary relationships among mobile genetic elements (MGEs) and between MGEs and their organismal hosts. Shown is a simplified depiction of the organismal evolutionary tree of life (inspired by references 249 and 250) outlining the two major supergroups of cellular life, *Bacteria* and *Archaea*, with eukaryotes evolving from (heimdallarchaeote) archaea. All organismal life relates to a last universal common ancestor (LUCA) located at the bottom of the trunk of the tree. In contrast, MGEs, the occupants of the virosphere, are polyphyletic and hence do not have a single LUCA. Hence, several individual evolutionary trees of MGEs need to be superimposed onto the cellular tree of life through the relationships of individual MGEs and their cellular hosts (here illustrated through the six currently establishes realms of viruses within the orthovirosphere and the less-defined space of the perivirosphere). Tobacco mosaic virus (TMV), enterobacteria phage PRD1, "phage lambda," Pyrobaculum filamentous virus 2 (PFV2), and phage ΦX174—among the first representatives of viral realms *Riboviria*, *Varidnaviria*, *Duplodnaviria*, *Adnaviria*, and *Monodnaviria*, respectively, and hence at the center of Fig. 1 as a starting point to operationally define "viruses"—occupy the periphery of the actual evolutionary cellular and MGE trees. For instance, phages PRD1, lambda, and ΦX174 as well as HK97 and MS2 all infect gammaproteobacterial *Enterobacteria* such as *Escherichia coli* and hence are located at the same location on the cellular tree of life albeit being completely unrelated to each other. On the other hand, TMV infects solanacean plants and hence is placed on the archaeplastid subbranch of Eukaryota, whereas human viruses (e.g., hepatitis delta virus 1 [HDV-1], herpes simplex virus [HSV-1], human immunodeficiency virus 1 [HIV-1], severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2], and variola virus [VARV]) are located at the same location on the ophistokont subbranch of Eukaryota. Porcine circovirus 2 (PCV-2) infects mammals different from humans (suids) and hence is located closely to the human viruses. Virus realms are depicted as branching lines with fading termini, as it is currently unclear when in evolutionary history each lineage began and which cellular tree branches they actually penetrate. For instance, duplodnaviriads infect bacteria, archaea, and mammalian eukaryotes, and hence it is likely that they occupy most of the cellular tree of life. On the other hand, adnaviriads have thus far only been found in a small number of crenarcheotes and, hence, here only occupy part of the cellular tree of life.

have lost the basic properties of semiautonomous replicators through domestication, such as members of "*Polydnaviriformidae*," GTAs, and tailocins, cannot be included in the perivirosphere or the replicator space itself, even though they clearly have retained ancestral virus features. Crucially, both the orthovirosphere and the perivirosphere are obligately host associated, and members of both adorn all the major branches of the tree of life (Fig. 3).

Having defined the orthovirosphere and perivirosphere, we are still left with the question of which replicators should be considered viruses, that is, only those within the orthovirosphere or all denizens of the orthovirosphere and perivirosphere. The simplest and fully consistent approach is to posit that all members of the orthovirosphere are viruses whereas those in the perivirosphere are "virus-like replicators." Alternatively, a conceptual definition of "virus" would admit most of such virus-like replicators. From this standpoint, an amended version of the Raoult-Forterre virus definition seems to make the most sense. Consequently, we formally proposed the following operational definition of virus to the ICTV.

> Viruses *sensu stricto* are defined operationally by the ICTV as a type of MGE that encodes at least one protein that is a major component of the virion encasing the nucleic acid of the respective MGE and therefore the gene encoding the major virion protein itself or MGEs that are clearly demonstrable to be members of a line of evolutionary descent of such major virion protein-encoding entities. Any monophyletic group of MGEs that originates from a virion protein-encoding ancestor should be classified as a group of viruses (73).

In November 2020, this definition was accepted by the ICTV Executive Committee and in March 2021, it was ratified, thereby becoming official. Most likely, this definition will have to be refined in the future, but it will serve as a starting point to further delineate the various boundaries in the replicator space.

APPENDIX

GLOSSARY

megataxonomy Classification of viruses into taxa at or above the order rank to reflect the known macroevolutionary relationships of large virus groups plus nomenclature for these megataxa (27).
mobile genetic element (MGE) A replicating genome with an autonomous evolutionary trajectory; used here interchangeably with replicator.
orthovirosphere (introduced here) The core of the virosphere, including typical viruses.
perivirosphere (introduced here) The periphery of the virosphere, including virus-like replicators that fit some but not all aspects of the definition of a virus.
polyphyletic Not being connected to a common ancestor.
replicator A replicating genome with an autonomous evolutionary trajectory; used here interchangeably with mobile genetic element (MGE).
reproducer A biological entity that reproduces its physical structure across generations (includes cellular organisms, mitochondria, chloroplasts, and some other types of plastids).
satellitid(s) Member(s) of a satellite nucleic acid family, *-satellitidae*.
-viran(s) Member(s) of a viral kingdom, *-virae*.
-viral(s) Member(s) of a viral order, *-virales*.
-viriad(s) Member(s) of a viral realm, *-viria*.
-viricete(s) Member(s) of a viral phylum, *-viricetes*.
-virid(s) Member(s) of a viral family, *-viridae* (251).
virosphere The entirety of viruses (orthovirosphere plus perivirosphere), the subset of replicators that fit the definition of a virus.

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REFERENCES

1. Moreira D, López-García P. 2009. Ten reasons to exclude viruses from the tree of life. Nat Rev Microbiol 7:306–311. https://doi.org/10.1038/nrmicro2108.
2. Forterre P, Prangishvili D. 2009. The great billion-year war between ribosome- and capsid-encoding organisms (cells and viruses) as the major source of evolutionary novelties. Ann N Y Acad Sci 1178:65–77. https://doi.org/10.1111/j.1749-6632.2009.04993.x.
3. Koonin EV, Dolja VV. 2013. A virocentric perspective on the evolution of life. Curr Opin Virol 3:546–557. https://doi.org/10.1016/j.coviro.2013.06.008.
4. Harris HMB, Hill C. 2020. A place for viruses on the tree of life. Front Microbiol 11:604048. https://doi.org/10.3389/fmicb.2020.604048.
5. López-García P. 2012. The place of viruses in biology in light of the metabolism- versus-replication-first debate. Hist Philos Life Sci 34:391–406.
6. Koonin EV. 2010. The two empires and three domains of life in the postgenomic age. Nat Educ 3:27.
7. Szathmáry E, Maynard Smith J. 1997. From replicators to reproducers: the first major transitions leading to life. J Theor Biol 187:555–571. https://doi.org/10.1006/jtbi.1996.0389.
8. Takeuchi N, Hogeweg P. 2007. The role of complex formation and deleterious mutations for the stability of RNA-like replicator systems. J Mol Evol 65:668–686. https://doi.org/10.1007/s00239-007-9044-6.
9. Iranzo J, Puigbò P, Lobkovsky AE, Wolf YI, Koonin EV. 2016. Inevitability of genetic parasites. Genome Biol Evol 8:2856–2869. https://doi.org/10.1093/gbe/evw193.
10. Koonin EV, Wolf YI, Katsnelson MI. 2017. Inevitability of the emergence and persistence of genetic parasites caused by evolutionary instability of parasite-free states. Biol Direct 12:31. https://doi.org/10.1186/s13062-017-0202-5.
11. Mushegian AR. 2020. Are there 10^{31} virus particles on earth, or more, or fewer? J Bacteriol 202:e00052-20. https://doi.org/10.1128/JB.00052-20.
12. Hendrix RW, Smith MC, Burns RN, Ford ME, Hatfull GF. 1999. Evolutionary relationships among diverse bacteriophages and prophages: all the world's a phage. Proc Natl Acad Sci U S A 96:2192–2197. https://doi.org/10.1073/pnas.96.5.2192.
13. Cobián Güemes AG, Youle M, Cantú VA, Felts B, Nulton J, Rohwer F. 2016. Viruses as winners in the game of life. Annu Rev Virol 3:197–214. https://doi.org/10.1146/annurev-virology-100114-054952.
14. Wigington CH, Sonderegger D, Brussaard CP, Buchan A, Finke JF, Fuhrman JA, Lennon JT, Middelboe M, Suttle CA, Stock C, Wilson WH, Wommack KE, Wilhelm SW, Weitz JS. 2016. Re-examination of the relationship between marine virus and microbial cell abundances. Nat Microbiol 1:15024. https://doi.org/10.1038/nmicrobiol.2015.24.
15. López-García P, Gutiérrez-Preciado A, Ciobanu M, Deschamps P, Jardillier L, López-Pérez M, Rodríguez-Valera F, Moreira D. 17 February 2021. Viral and parasitic cell ratios per free-living microbe across ecosystems. bioRxiv https://doi.org/10.1101/2021.02.17.431581.
16. Aziz RK, Breitbart M, Edwards RA. 2010. Transposases are the most abundant, most ubiquitous genes in nature. Nucleic Acids Res 38:4207–4217. https://doi.org/10.1093/nar/gkq140.
17. Kazazian HH, Jr. 2004. Mobile elements: drivers of genome evolution. Science 303:1626–1632. https://doi.org/10.1126/science.1089670.
18. Gogvadze E, Buzdin A. 2009. Retroelements and their impact on genome evolution and functioning. Cell Mol Life Sci 66:3727–3742. https://doi.org/10.1007/s00018-009-0107-2.
19. Brüssow H. 2009. The not so universal tree of life or the place of viruses in the living world. Philos Trans R Soc Lond B Biol Sci 364:2263–2274. https://doi.org/10.1098/rstb.2009.0036.
20. Kristensen DM, Waller AS, Yamada T, Bork P, Mushegian AR, Koonin EV. 2013. Orthologous gene clusters and taxon signature genes for viruses of prokaryotes. J Bacteriol 195:941–950. https://doi.org/10.1128/JB.01801-12.
21. Rohwer F, Prangishvili D, Lindell D. 2009. Roles of viruses in the environment. Environ Microbiol 11:2771–2774. https://doi.org/10.1111/j.1462-2920.2009.02101.x.
22. Rohwer F, Thurber RV. 2009. Viruses manipulate the marine environment. Nature 459:207–212. https://doi.org/10.1038/nature08060.
23. Comeau AM, Krisch HM. 2005. War is peace–dispatches from the bacterial and phage killing fields. Curr Opin Microbiol 8:488–494. https://doi.org/10.1016/j.mib.2005.06.004.
24. Danovaro R, Dell'Anno A, Corinaldesi C, Rastelli E, Cavicchioli R, Krupovic M, Noble RT, Nunoura T, Prangishvili D. 2016. Virus-mediated archaeal hecatomb in the deep seafloor. Sci Adv 2:e1600492. https://doi.org/10.1126/sciadv.1600492.
25. Baltimore D. 1971. Expression of animal virus genomes. Bacteriol Rev 35:235–241. https://doi.org/10.1128/br.35.3.235-241.1971.
26. Agol VI. 1974. Towards the system of viruses. Biosystems 6:113–132. https://doi.org/10.1016/0303-2647(74)90003-3.
27. Koonin EV, Dolja VV, Krupovic M, Varsani A, Wolf YI, Yutin N, Zerbini FM, Kuhn JH. 2020. Global organization and proposed megataxonomy of the virus world. Microbiol Mol Biol Rev 84:e00061-19. https://doi.org/10.1128/MMBR.00061-19.
28. Koonin EV, Starokadomskyy P. 2016. Are viruses alive? The replicator paradigm sheds decisive light on an old but misguided question. Stud Hist Philos Biol Biomed Sci 59:125–134. https://doi.org/10.1016/j.shpsc.2016.02.016.
29. Koonin EV, Makarova KS, Wolf YI, Krupovic M. 2020. Evolutionary entanglement of mobile genetic elements and host defence systems: guns for hire. Nat Rev Genet 21:119–131. https://doi.org/10.1038/s41576-019-0172-9.
30. Kristensen DM, Mushegian AR, Dolja VV, Koonin EV. 2010. New dimensions of the virus world discovered through metagenomics. Trends Microbiol 18:11–19. https://doi.org/10.1016/j.tim.2009.11.003.
31. Simmonds P, Adams MJ, Benkő M, Breitbart M, Brister JR, Carstens EB, Davison AJ, Delwart E, Gorbalenya AE, Harrach B, Hull R, King AMQ, Koonin EV, Krupovic M, Kuhn JH, Lefkowitz EJ, Nibert ML, Orton R, Roossinck MJ, Sabanadzovic S, Sullivan MB, Suttle CA, Tesh RB, van der Vlugt RA, Varsani A, Zerbini FM. 2017. Consensus statement: virus taxonomy in the age of metagenomics. Nat Rev Microbiol 15:161–168. https://doi.org/10.1038/nrmicro.2016.177.
32. Anonymous. 2021. virus (n.). https://www.etymonline.com/word/virus.
33. Trevisa J. 1398. Translation of Bartholomeus Anglicus's De Proprietatibus Rerum.
34. Iwanowsky D. 1892. Über die Mosaikkrankheit der Tabakspflanze. Sci Bull Imp Acad Sci St Petersburg 35:67–70.
35. Beijerinck MW. 1898. Over een Contagium vivum fluidum als oorzaak van de Vlekziekte der Tabaksbladen. Verhandelingen VII:229–235.
36. Scholthof KB. 2004. Tobacco mosaic virus: a model system for plant biology. Annu Rev Phytopathol 42:13–34. https://doi.org/10.1146/annurev.phyto.42.040803.140322.
37. Loeffler F, Frosch P. 1897. Summarischer Bericht über die Ergebisse der Untersuchungen der Kommission zur Erforschung der Maul- und Klauenseuche bei dem Institute für Infektionskrankheiten in Berlin. Centralbl Bakteriol Parasitenkd Infektionskr Erste Abt Med-Hyg Bakteriol Tier Parasitenkd XXII:257–259.
38. Loeffler F. 1898. Berichte der Kommission zur Erforschung der Maul- und Klauenseuche bei dem Institut für Infektionskrankheiten in Berlin. Centralbl Bakteriol Parasitenkd Infektionskr Erste Abt Med-Hygienische Bakteriol Tier Parasitenkd XXIII:371–391.
39. Reed W, Carroll J, Agramonte A, Lazear JW. 1900. The etiology of yellow fever. A preliminary note. Public Health Pap Rep 26:37–53.
40. d'Herelle MF. 1917. Sur un microbe invisible antagoniste des bacilles dysentériques. C R Hebd Séances Acad Sci 165:373–375.
41. Stanley WM. 1935. Isolation of a crystalline protein possessing the properties of tobacco-mosaic virus. Science 81:644–645. https://doi.org/10.1126/science.81.2113.644.
42. Kausche GA, Pfankuch E, Ruska H. 1939. Die Sichtbarmachung von pflanzlichem Virus im Übermikroskop. Naturwissenschaften 27:292–299. https://doi.org/10.1007/BF01493353.
43. Bennett CW. 1939. The nomenclature of plant viruses. Phytopathology 29:422–430.
44. Bawden FC. 1941. Nomina ad infinitum. Chron Bot 6:17–18.
45. Brandes J, Wetter C. 1959. Classification of elongated plant viruses on the basis of particle morphology. Virology 8:99–115. https://doi.org/10.1016/0042-6822(59)90022-4.
46. Bradley DE. 1965. The morphology and physiology of bacteriophages as revealed by the electron microscope. J R Microsc Soc 84:257–316.
47. Holmes FO. 1948. Order *Virales* - the filterable viruses, p 1125–1286. *In* Breed RS, Murray EGD, Hitchens AP (ed), Bergey's manual of determinative bacteriology, 6th ed. The Williams & Wilkins Company, Baltimore, MD.
48. Cooper PD. 1961. A chemical basis for the classification of animal viruses. Nature 190:302–305. https://doi.org/10.1038/190302a0.
49. Hamparian VV, Hilleman MR, Ketler A. 1963. Contributions to characterization and classification of animal viruses. Proc Soc Exp Biol Med 112:1040–1050. https://doi.org/10.3181/00379727-112-28247.
50. Wildy P. 1962. Classifying viruses at higher levels: symmetry and structure of virus particles as criteria. Symp Soc Gen Microbiol XII:145–163.

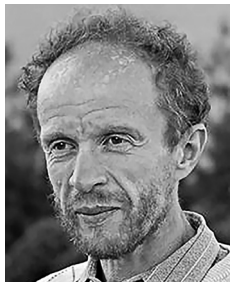
51. Horne RW, Wildy P. 1961. Symmetry in virus architecture. Virology 15:348–373. https://doi.org/10.1016/0042-6822(61)90366-x.
52. Tauraso NM, Shelokov A. 1967. Arboviruses – a problem in classification. Arch Gesamte Virusforsch 22:273–279. https://doi.org/10.1007/BF01240522.
53. Lwoff A, Horne R, Tournier P. 1962. A system of viruses. Cold Spring Harbor Symp Quant Biol 27:51–55. https://doi.org/10.1101/sqb.1962.027.001.008.
54. Lwoff A, Horne RW, Tournier P. 1962. Un système des virus. C R Hebd Seances Acad Sci 254:4225–4227.
55. Lwoff A, Tournier P. 1966. The classification of viruses. Annu Rev Microbiol 20:45–74. https://doi.org/10.1146/annurev.mi.20.100166.000401.
56. Lwoff A. 1957. The concept of virus. J Gen Microbiol 17:239–253. https://doi.org/10.1099/00221287-17-2-239.
57. Diener TO, Raymer WB. 1967. Potato spindle tuber virus: a plant virus with properties of a free nucleic acid. Science 158:378–381. https://doi.org/10.1126/science.158.3799.378.
58. Diener TO. 1971. Potato spindle tuber "virus". IV. A replicating, low molecular weight RNA. Virology 45:411–428. https://doi.org/10.1016/0042-6822(71)90342-4.
59. Abergel C, Claverie JM. 2020. Giant viruses. Curr Biol 30:R1108–R1110. https://doi.org/10.1016/j.cub.2020.08.055.
60. Koonin EV, Yutin N. 2019. Evolution of the large nucleocytoplasmic DNA viruses of eukaryotes and convergent origins of viral gigantism. Adv Virus Res 103:167–202. https://doi.org/10.1016/bs.aivir.2018.09.002.
61. Colson P, La Scola B, Raoult D. 2017. Giant viruses of amoebae: a journey through innovative research and paradigm changes. Annu Rev Virol 4:61–85. https://doi.org/10.1146/annurev-virology-101416-041816.
62. Raoult D, Forterre P. 2008. Redefining viruses: lessons from mimivirus. Nat Rev Microbiol 6:315–319. https://doi.org/10.1038/nrmicro1858.
63. Claverie JM, Abergel C. 2016. Giant viruses: the difficult breaking of multiple epistemological barriers. Stud Hist Philos Biol Biomed Sci 59:89–99. https://doi.org/10.1016/j.shpsc.2016.02.015.
64. Nasir A, Romero-Severson E, Claverie JM. 2020. Investigating the concept and origin of viruses. Trends Microbiol 28:959–967. https://doi.org/10.1016/j.tim.2020.08.003.
65. Ghabrial SA, Castón JR, Jiang D, Nibert ML, Suzuki N. 2015. 50-plus years of fungal viruses. Virology 479–480:356–368. https://doi.org/10.1016/j.virol.2015.02.034.
66. Hillman BI, Annisa A, Suzuki N. 2018. Viruses of plant-interacting fungi. Adv Virus Res 100:99–116. https://doi.org/10.1016/bs.aivir.2017.10.003.
67. Nibert ML, Tang J, Xie J, Collier AM, Ghabrial SA, Baker TS, Tao YJ. 2013. 3D structures of fungal partitiviruses. Adv Virus Res 86:59–85. https://doi.org/10.1016/B978-0-12-394315-6.00003-9.
68. Dolja VV, Krupovic M, Koonin EV. 2020. Deep roots and splendid boughs of the global plant virome. Annu Rev Phytopathol 58:23–53. https://doi.org/10.1146/annurev-phyto-030320-041346.
69. Mager DL, Stoye JP. 2015. Mammalian endogenous retroviruses. Microbiol Spectr 3:MDNA3-0009-2014. https://doi.org/10.1128/microbiolspec.MDNA3-0009-2014.
70. Johnson WE. 2019. Origins and evolutionary consequences of ancient endogenous retroviruses. Nat Rev Microbiol 17:355–370. https://doi.org/10.1038/s41579-019-0189-2.
71. Herniou EA, Huguet E, Thézé J, Bézier A, Periquet G, Drezen JM. 2013. When parasitic wasps hijacked viruses: genomic and functional evolution of polydnaviruses. Philos Trans R Soc Lond B Biol Sci 368:20130051. https://doi.org/10.1098/rstb.2013.0051.
72. Drezen JM, Leobold M, Bézier A, Huguet E, Volkoff AN, Herniou EA. 2017. Endogenous viruses of parasitic wasps: variations on a common theme. Curr Opin Virol 25:41–48. https://doi.org/10.1016/j.coviro.2017.07.002.
73. Kuhn JH, Dolja VV, Krupovic M, Adriaenssens EM, Di Serio F, Dutilh BE, Flores R, Harrach B, Mushegian A, Owens B, Randles J, Rubino L, Sabanadzovic S, Simmonds P, Varsani A, Zerbini M, Koonin EV. 2021. Expand, amend, and emend the International Code of Virus Classification and Nomenclature (ICVCN; "the Code") and the statutes to clearly define the remit of the ICTV. International Committee for Taxonomy of Viruses proposal (Taxoprop) number 2020.005G. https://doi.org/10.13140/RG.2.2.26202.26565.
74. Medawar PB, Medawar JS. 1983. Aristotle to Zeus, a philosophical dictionary of biology. Harvard University Press, Cambridge, MA.
75. Dolja VV. 2021. Rapid emergence of virus-host mutualism under stress. Proc Natl Acad Sci U S A 118:e2100936118. https://doi.org/10.1073/pnas.2100936118.
76. González R, Butković A, Escaray FJ, Martínez-Latorre J, Melero Í, Pérez-Parets E, Gómez-Cadenas A, Carrasco P, Elena SF. 2021. Plant virus evolution under strong drought conditions results in a transition from parasitism to mutualism. Proc Natl Acad Sci U S A 118:e2020990118. https://doi.org/10.1073/pnas.2020990118.
77. Márquez LM, Redman RS, Rodriguez RJ, Roossinck MJ. 2007. A virus in a fungus in a plant: three-way symbiosis required for thermal tolerance. Science 315:513–515. https://doi.org/10.1126/science.1136237.
78. Herrero-Uribe L. 2011. Viruses, definitions and reality. Rev Biol Trop 59:993–998.
79. Koonin EV, Dolja VV, Krupovic M. 2021. The healthy human virome: from virus-host symbiosis to disease. Curr Opin Virol 47:86–94. https://doi.org/10.1016/j.coviro.2021.02.002.
80. Bândea CI. 1983. A new theory on the origin and the nature of viruses. J Theor Biol 105:591–602. https://doi.org/10.1016/0022-5193(83)90221-7.
81. Claverie JM. 2006. Viruses take center stage in cellular evolution. Genome Biol 7:110. https://doi.org/10.1186/gb-2006-7-6-110.
82. Forterre P. 2013. The virocell concept and environmental microbiology. ISME J 7:233–236. https://doi.org/10.1038/ismej.2012.110.
83. Forterre P. 2017. Viruses in the 21st Century: from the curiosity-driven discovery of giant viruses to new concepts and definition of life. Clin Infect Dis 65:S74–S79. https://doi.org/10.1093/cid/cix349.
84. Forterre P. 2016. To be or not to be alive: how recent discoveries challenge the traditional definitions of viruses and life. Stud Hist Philos Biol Biomed Sci 59:100–108. https://doi.org/10.1016/j.shpsc.2016.02.013.
85. Abrahão J, Silva L, Silva LS, Khalil JYB, Rodrigues R, Arantes T, Assis F, Boratto P, Andrade M, Kroon EG, Ribeiro B, Bergier I, Seligmann H, Ghigo E, Colson P, Levasseur A, Kroemer G, Raoult D, La Scola B. 2018. Tailed giant tupanvirus possesses the most complete translational apparatus of the known virosphere. Nat Commun 9:749. https://doi.org/10.1038/s41467-018-03168-1.
86. Legendre M, Fabre E, Poirot O, Jeudy S, Lartigue A, Alempic JM, Beucher L, Philippe N, Bertaux L, Christo-Foroux E, Labadie K, Couté Y, Abergel C, Claverie JM. 2018. Diversity and evolution of the emerging *Pandoraviridae* family. Nat Commun 9:2285. https://doi.org/10.1038/s41467-018-04698-4.
87. Philippe N, Legendre M, Doutre G, Couté Y, Poirot O, Lescot M, Arslan D, Seltzer V, Bertaux L, Bruley C, Garin J, Claverie JM, Abergel C. 2013. Pandoraviruses: amoeba viruses with genomes up to 2.5 Mb reaching that of parasitic eukaryotes. Science 341:281–286. https://doi.org/10.1126/science.1239181.
88. Claverie JM, Ogata H, Audic S, Abergel C, Suhre K, Fournier P-E. 2006. Mimivirus and the emerging concept of "giant" virus. Virus Res 117:133–144. https://doi.org/10.1016/j.virusres.2006.01.008.
89. Raoult D. 2013. TRUC or the need for a new microbial classification. Intervirology 56:349–353. https://doi.org/10.1159/000354269.
90. Colson P, Levasseur A, La Scola B, Sharma V, Nasir A, Pontarotti P, Caetano-Anollés G, Raoult D. 2018. Ancestrality and mosaicism of giant viruses supporting the definition of the fourth TRUC of microbes. Front Microbiol 9:2668. https://doi.org/10.3389/fmicb.2018.02668.
91. Lwoff A, Anderson TF, Jacob F. 1959. Remarques sur les caractéristiques de la particule virale infectieuse. Ann Inst Pasteur 97:281–289.
92. Battaglia E. 2007. Virology: terms and etymology. Atti Soc Tosc Sci Nat Mem Ser B 114:141–153.
93. Caspar DL, Klug A. 1962. Physical principles in the construction of regular viruses. Cold Spring Harbor Symp Quant Biol 27:1–24. https://doi.org/10.1101/sqb.1962.027.001.005.
94. Krupovic M, Koonin EV. 2017. Multiple origins of viral capsid proteins from cellular ancestors. Proc Natl Acad Sci U S A 114:E2401–E2410. https://doi.org/10.1073/pnas.1621061114.
95. Forterre P, Krupovic M, Prangishvili D. 2014. Cellular domains and viral lineages. Trends Microbiol 22:554–558. https://doi.org/10.1016/j.tim.2014.07.004.
96. Lang AS, Zhaxybayeva O, Beatty JT. 2012. Gene transfer agents: phage-like elements of genetic exchange. Nat Rev Microbiol 10:472–482. https://doi.org/10.1038/nrmicro2802.
97. Shakya M, Soucy SM, Zhaxybayeva O. 2017. Insights into origin and evolution of α-proteobacterial gene transfer agents. Virus Evol 3:vex036. https://doi.org/10.1093/ve/vex036.
98. Lang AS, Westbye AB, Beatty JT. 2017. The distribution, evolution, and roles of gene transfer agents in prokaryotic genetic exchange. Annu Rev Virol 4:87–104. https://doi.org/10.1146/annurev-virology-101416-041624.
99. Bárdy P, Füzik T, Hrebík D, Pantůček R, Thomas Beatty J, Plevka P. 2020. Structure and mechanism of DNA delivery of a gene transfer agent. Nat Commun 11:3034. https://doi.org/10.1038/s41467-020-16669-9.
100. Esterman ES, Wolf YI, Kogay R, Koonin EV, Zhaxybayeva O. 2021. Evolution of DNA packaging in gene transfer agents. Virus Evol 7:veab015. https://doi.org/10.1093/ve/veab015.

101. Rodrigues RAL, da Silva LCF, Abrahão JS. 2020. Translating the language of giants: translation-related genes as a major contribution of giant viruses to the virosphere. Arch Virol 165:1267–1278. https://doi.org/10.1007/s00705-020-04626-2.
102. Schulz F, Yutin N, Ivanova NN, Ortega DR, Lee TK, Vierheilig J, Daims H, Horn M, Wagner M, Jensen GJ, Kyrpides NC, Koonin EV, Woyke T. 2017. Giant viruses with an expanded complement of translation system components. Science 356:82–85. https://doi.org/10.1126/science.aal4657.
103. Mizuno CM, Guyomar C, Roux S, Lavigne R, Rodriguez-Valera F, Sullivan MB, Gillet R, Forterre P, Krupovic M. 2019. Numerous cultivated and uncultivated viruses encode ribosomal proteins. Nat Commun 10:752. https://doi.org/10.1038/s41467-019-08672-6.
104. Kazlauskas D, Krupovic M, Venclovas Č. 2016. The logic of DNA replication in double-stranded DNA viruses: insights from global analysis of viral genomes. Nucleic Acids Res 44:4551–4564. https://doi.org/10.1093/nar/gkw322.
105. Philosof A, Yutin N, Flores-Uribe J, Sharon I, Koonin EV, Béjà O. 2017. Novel abundant oceanic viruses of uncultured marine group II *Euryarchaeota*. Curr Biol 27:1362–1368. https://doi.org/10.1016/j.cub.2017.03.052.
106. Gaudin M, Krupovic M, Marguet E, Gauliard E, Cvirkaite-Krupovic V, Le Cam E, Oberto J, Forterre P. 2014. Extracellular membrane vesicles harbouring viral genomes. Environ Microbiol 16:1167–1175. https://doi.org/10.1111/1462-2920.12235.
107. Liu J, Cvirkaite-Krupovic V, Commere P-H, Yang Y, Zhou F, Forterre P, Shen Y, Krupovic M. 26 April 2021. Archaeal extracellular vesicles are produced in an ESCRT-dependent manner and promote gene transfer and nutrient cycling in extreme environments. ISME J https://doi.org/10.1038/s41396-021-00984-0.
108. Hackl T, Laurenceau R, Ankenbrand MJ, Bliem C, Cariani Z, Thomas E, Dooley KD, Arellano AA, Hogle SL, Berube P, Leventhal GE, Luo E, Eppley J, Zayed AA, Beaulaurier J, Stepanauskas R, Sullivan MB, DeLong EF, Biller SJ, Chisholm SW. 28 December 2020. Novel integrative elements and genomic plasticity in ocean ecosystems. bioRxiv https://doi.org/10.1101/2020.12.28.424599.
109. Kawamura Y, Yamamoto Y, Sato TA, Ochiya T. 2017. Extracellular vesicles as trans-genomic agents: emerging roles in disease and evolution. Cancer Sci 108:824–830. https://doi.org/10.1111/cas.13222.
110. Kawamura Y, Sanchez Calle A, Yamamoto Y, Sato TA, Ochiya T. 2019. Extracellular vesicles mediate the horizontal transfer of an active LINE-1 retrotransposon. J Extracell Vesicles 8:1643214. https://doi.org/10.1080/20013078.2019.1643214.
111. Erdmann S, Tschitschko B, Zhong L, Raftery MJ, Cavicchioli R. 2017. A plasmid from an Antarctic haloarchaeon uses specialized membrane vesicles to disseminate and infect plasmid-free cells. Nat Microbiol 2:1446–1455. https://doi.org/10.1038/s41564-017-0009-2.
112. Blanc-Mathieu R, Dahle H, Hofgaard A, Brandt D, Ban H, Kalinowski J, Ogata H, Sandaa RA. 2021. A persistent giant algal virus, with a unique morphology, encodes an unprecedented number of genes involved in energy metabolism. J Virol 95:e02446-20. https://doi.org/10.1128/JVI.02446-20.
113. Aherfi S, Brahim Belhaouari D, Pinault L, Baudoin J-P, Decloquement P, Abrahao J, Colson P, Levasseur A, Lamb DC, Chabriere E, Raoult D, La Scola B. 21 September 2020. Tricarboxylic acid cycle and proton gradient in *Pandoravirus massiliensis*: is it still a virus? bioRxiv https://doi.org/10.1101/2020.09.21.306415.
114. Puxty RJ, Millard AD, Evans DJ, Scanlan DJ. 2015. Shedding new light on viral photosynthesis. Photosynth Res 126:71–97. https://doi.org/10.1007/s11120-014-0057-x.
115. Fridman S, Flores-Uribe J, Larom S, Alalouf O, Liran O, Yacoby I, Salama F, Bailleul B, Rappaport F, Ziv T, Sharon I, Cornejo-Castillo FM, Philosof A, Dupont CL, Sánchez P, Acinas SG, Rohwer FL, Lindell D, Béjà O. 2017. A myovirus encoding both photosystem I and II proteins enhances cyclic electron flow in infected *Prochlorococcus* cells. Nat Microbiol 2:1350–1357. https://doi.org/10.1038/s41564-017-0002-9.
116. Roux S, Krupovic M, Debroas D, Forterre P, Enault F. 2013. Assessment of viral community functional potential from viral metagenomes may be hampered by contamination with cellular sequences. Open Biol 3:130160. https://doi.org/10.1098/rsob.130160.
117. Szathmáry E. 2006. The origin of replicators and reproducers. Philos Trans R Soc Lond B Biol Sci 361:1761–1776. https://doi.org/10.1098/rstb.2006.1912.
118. Koonin EV. 2014. The origins of cellular life. Antonie Van Leeuwenhoek 106:27–41. https://doi.org/10.1007/s10482-014-0169-5.
119. Dawkins R. 1976. The selfish gene. Oxford University Press, Oxford, UK.
120. Fraile A, García-Arenal F. 2018. Tobamoviruses as models for the study of virus evolution. Adv Virus Res 102:89–117. https://doi.org/10.1016/bs.aivir.2018.06.006.
121. Dobzhansky T. 1973. Nothing in biology makes sense except in the light of evolution. Am Biol Techer 35:125–129. https://doi.org/10.2307/4444260.
122. Krupovic M, Kuhn JH, Wang F, Baquero DP, Dolja VV, Egelman EH, Prangishvili D, Koonin EV. 2021. *Adnaviria*: a new realm for archaeal filamentous viruses with linear A-form double-stranded DNA genomes. J Virol. 95:e00673-21. https://doi.org/10.1128/JVI.00673-21.
123. Hepojoki J, Hetzel U, Paraskevopoulou S, Drosten C, Harrach B, Zerbini M, Koonin EV, Krupovic M, Dolja V, Kuhn JH. 2021. Create one new realm (*Ribozyviria*) including one new family (*Kolmioviridae*) including genus *Deltavirus* and seven new genera for a total of 15 species. International Committee for Taxonomy of Viruses proposal (Taxoprop) number 2020.012D. https://doi.org/10.13140/RG.2.2.31235.43041.
124. Cui J, Li F, Shi ZL. 2019. Origin and evolution of pathogenic coronaviruses. Nat Rev Microbiol 17:181–192. https://doi.org/10.1038/s41579-018-0118-9.
125. Shi M, Lin XD, Vasilakis N, Tian JH, Li CX, Chen LJ, Eastwood G, Diao XN, Chen MH, Chen X, Qin XC, Widen SG, Wood TG, Tesh RB, Xu J, Holmes EC, Zhang YZ. 2016. Divergent viruses discovered in arthropods and vertebrates revise the evolutionary history of the *Flaviviridae* and related viruses. J Virol 90:659–669. https://doi.org/10.1128/JVI.02036-15.
126. Dolja VV, Kreuze JF, Valkonen JP. 2006. Comparative and functional genomics of closteroviruses. Virus Res 117:38–51. https://doi.org/10.1016/j.virusres.2006.02.002.
127. Shi M, Lin XD, Tian JH, Chen LJ, Chen X, Li CX, Qin XC, Li J, Cao JP, Eden JS, Buchmann J, Wang W, Xu J, Holmes EC, Zhang YZ. 2016. Redefining the invertebrate RNA virosphere. Nature 540:539–543. https://doi.org/10.1038/nature20167.
128. Yong CY, Yeap SK, Omar AR, Tan WS. 2017. Advances in the study of nodavirus. PeerJ 5:e3841. https://doi.org/10.7717/peerj.3841.
129. Krupovic M, Kuhn JH, Fischer MG. 2016. A classification system for virophages and satellite viruses. Arch Virol 161:233–247. https://doi.org/10.1007/s00705-015-2622-9.
130. Ban N, Larson SB, McPherson A. 1995. Structural comparison of the plant satellite viruses. Virology 214:571–583. https://doi.org/10.1006/viro.1995.0068.
131. Li K, Zheng D, Cheng J, Chen T, Fu Y, Jiang D, Xie J. 2016. Characterization of a novel *Sclerotinia sclerotiorum* RNA virus as the prototype of a new proposed family within the order *Tymovirales*. Virus Res 219:92–99. https://doi.org/10.1016/j.virusres.2015.11.019.
132. Roossinck MJ, Sabanadzovic S, Okada R, Valverde RA. 2011. The remarkable evolutionary history of endornaviruses. J Gen Virol 92:2674–2678. https://doi.org/10.1099/vir.0.034702-0.
133. Fukuhara T. 2019. Endornaviruses: persistent dsRNA viruses with symbiotic properties in diverse eukaryotes. Virus Genes 55:165–173. https://doi.org/10.1007/s11262-019-01635-5.
134. Bian R, Andika IB, Pang T, Lian Z, Wei S, Niu E, Wu Y, Kondo H, Liu X, Sun L. 2020. Facilitative and synergistic interactions between fungal and plant viruses. Proc Natl Acad Sci U S A 117:3779–3788. https://doi.org/10.1073/pnas.1915996117.
135. Dawe AL, Nuss DL. 2013. Hypovirus molecular biology: from Koch's postulates to host self-recognition genes that restrict virus transmission, p 109–147. *In* Ghabrial SA (ed), Mycoviruses. Advances in virus research, vol 86. Academic Press, New York, NY.
136. Callanan J, Stockdale SR, Adriaenssens EM, Kuhn JH, Pallen M, Rumnieks J, Shkoporov A, Draper LA, Ross RP, Hill C. 2021. Rename one class (*Leviviricetes* - formerly *Allassoviricetes*), rename one order (*Norzivirales* - formerly *Levivirales*), create one new order (*Timlovirales*), and expand the class to a total of six families, 420 genera and 883 species. International Committee for Taxonomy of Viruses proposal (Taxoprop) number 2020.095B. https://doi.org/10.13140/RG.2.2.25363.40481.
137. Bruenn JA, Warner BE, Yerramsetty P. 2015. Widespread mitovirus sequences in plant genomes. PeerJ 3:e876. https://doi.org/10.7717/peerj.876.
138. Taliansky ME, Robinson DJ. 2003. Molecular biology of umbraviruses: phantom warriors. J Gen Virol 84:1951–1960. https://doi.org/10.1099/vir.0.19219-0.
139. Wolf YI, Kazlauskas D, Iranzo J, Lucía-Sanz A, Kuhn JH, Krupovic M, Dolja VV, Koonin EV. 2018. Origins and evolution of the global RNA virome. mBio 9:e02329-18. https://doi.org/10.1128/mBio.02329-18.
140. Koonin EV, Dolja VV. 2014. Virus world as an evolutionary network of viruses and capsidless selfish elements. Microbiol Mol Biol Rev 78:278–303. https://doi.org/10.1128/MMBR.00049-13.

141. Gladyshev EA, Arkhipova IR. 2011. A widespread class of reverse transcriptase-related cellular genes. Proc Natl Acad Sci U S A 108:20311–20316. https://doi.org/10.1073/pnas.1100266108.
142. Krupovic M, Blomberg J, Coffin JM, Dasgupta I, Fan H, Geering AD, Gifford R, Harrach B, Hull R, Johnson W, Kreuze JF, Lindemann D, Llorens C, Lockhart B, Mayer J, Muller E, Olszewski NE, Pappu HR, Pooggin MM, Richert-Pöggeler KR, Sabanadzovic S, Sanfaçon H, Schoelz JE, Seal S, Stavolone L, Stoye JP, Teycheney PY, Tristem M, Koonin EV, Kuhn JH. 2018. *Ortervirales*: new virus order unifying five families of reverse-transcribing viruses. J Virol 92:e00515-18. https://doi.org/10.1128/JVI.00515-18.
143. Krupovic M, Koonin EV. 2017. Homologous capsid proteins testify to the common ancestry of retroviruses, caulimoviruses, pseudoviruses, and metaviruses. J Virol 91:e00210-17. https://doi.org/10.1128/JVI.00210-17.
144. Llorens C, Futami R, Covelli L, Domínguez-Escribá L, Viu JM, Tamarit D, Aguilar-Rodríguez J, Vicente-Ripolles M, Fuster G, Bernet GP, Maumus F, Munoz-Pomer A, Sempere JM, Latorre A, Moya A. 2011. The Gypsy Database (GyDB) of mobile genetic elements: release 2.0. Nucleic Acids Res 39:D70–D74. https://doi.org/10.1093/nar/gkq1061.
145. Llorens C, Soriano B, Krupovic M, ICTV Report Consortium. 2021. ICTV virus taxonomy profile: *Pseudoviridae*. J Gen Virol 102:001563. https://doi.org/10.1099/jgv.0.001563.
146. Llorens C, Soriano B, Krupovic M, ICTV Report Consortium. 2020. ICTV virus taxonomy profile: *Metaviridae*. J Gen Virol 101:1131–1132. https://doi.org/10.1099/jgv.0.001509.
147. Kim A, Terzian C, Santamaria P, Pélisson A, Purd'homme N, Bucheton A. 1994. Retroviruses in invertebrates: the *gypsy* retrotransposon is apparently an infectious retrovirus of *Drosophila melanogaster*. Proc Natl Acad Sci U S A 91:1285–1289. https://doi.org/10.1073/pnas.91.4.1285.
148. Lusic M, Siliciano RF. 2017. Nuclear landscape of HIV-1 infection and integration. Nat Rev Microbiol 15:69–82. https://doi.org/10.1038/nrmicro.2016.162.
149. Krupovic M. 2013. Networks of evolutionary interactions underlying the polyphyletic origin of ssDNA viruses. Curr Opin Virol 3:578–586. https://doi.org/10.1016/j.coviro.2013.06.010.
150. Kazlauskas D, Varsani A, Koonin EV, Krupovic M. 2019. Multiple origins of prokaryotic and eukaryotic single-stranded DNA viruses from bacterial and archaeal plasmids. Nat Commun 10:3425. https://doi.org/10.1038/s41467-019-11433-0.
151. Krupovic M, Varsani A, Kazlauskas D, Breitbart M, Delwart E, Rosario K, Yutin N, Wolf YI, Harrach B, Zerbini FM, Dolja VV, Kuhn JH, Koonin EV. 2020. *Cressdnaviricota*: a virus phylum unifying seven families of Rep-encoding viruses with single-stranded, circular DNA genomes. J Virol 94:e00582-20. https://doi.org/10.1128/JVI.00582-20.
152. Briddon RW, Martin DP, Roumagnac P, Navas-Castillo J, Fiallo-Olivé E, Moriones E, Lett J-M, Zerbini FM, Varsani A. 2018. *Alphasatellitidae*: a new family with two subfamilies for the classification of geminivirus- and nanovirus-associated alphasatellites. Arch Virol 163:2587–2600. https://doi.org/10.1007/s00705-018-3854-2.
153. Zhao L, Rosario K, Breitbart M, Duffy S. 2019. Eukaryotic circular Rep-encoding single-stranded DNA (CRESS DNA) viruses: ubiquitous viruses with small genomes and a diverse host range. Adv Virus Res 103:71–133. https://doi.org/10.1016/bs.aivir.2018.10.001.
154. Gronenborn B, Randles JW, Vetten HJ, Thomas JE. 2021. Create one new family (*Metaxyviridae*) with one new genus (*Cofodevirus*) and one species (*Coconut foliar decay virus*) moved from the family Nanoviridae (*Mulpavirales*). International Committee for Taxonomy of Viruses proposal (Taxoprop) number 2020.022P.
155. Gronenborn B, Randles JW, Knierim D, Barrière Q, Vetten HJ, Warthmann N, Cornu D, Sileye T, Winter S, Timchenko T. 2018. Analysis of DNAs associated with coconut foliar decay disease implicates a unique single-stranded DNA virus representing a new taxon. Sci Rep 8:5698. https://doi.org/10.1038/s41598-018-23739-y.
156. Colson P, Ominami Y, Hisada A, La Scola B, Raoult D. 2019. Giant mimiviruses escape many canonical criteria of the virus definition. Clin Microbiol Infect 25:147–154. https://doi.org/10.1016/j.cmi.2018.09.010.
157. Legendre M, Bartoli J, Shmakova L, Jeudy S, Labadie K, Adrait A, Lescot M, Poirot O, Bertaux L, Bruley C, Couté Y, Rivkina E, Abergel C, Claverie JM. 2014. Thirty-thousand-year-old distant relative of giant icosahedral DNA viruses with a pandoravirus morphology. Proc Natl Acad Sci U S A 111:4274–4279. https://doi.org/10.1073/pnas.1320670111.
158. Pereira Andrade A, Victor de Miranda Boratto P, Rodrigues RAL, Bastos TM, Azevedo BL, Dornas FP, Oliveira DB, Drumond BP, Kroon EG, Abrahão JS. 2019. New isolates of pandoraviruses: contribution to the study of replication cycle steps. J Virol 93:e01942-18. https://doi.org/10.1128/JVI.01942-18.
159. Rodrigues RAL, Andreani J, Andrade A, Machado TB, Abdi S, Levasseur A, Abrahão JS, La Scola B. 2018. Morphologic and genomic analyses of new isolates reveal a second lineage of cedratviruses. J Virol 92:e00372-18. https://doi.org/10.1128/JVI.00372-18.
160. Andreani J, Khalil JYB, Baptiste E, Hasni I, Michelle C, Raoult D, Levasseur A, La Scola B. 2017. Orpheovirus IHUMI-LCC2: a new virus among the giant viruses. Front Microbiol 8:2643. https://doi.org/10.3389/fmicb.2017.02643.
161. Krupovic M, Yutin N, Koonin E. 2020. Evolution of a major virion protein of the giant pandoraviruses from an inactivated bacterial glycoside hydrolase. Virus Evol 6:veaa059. https://doi.org/10.1093/ve/veaa059.
162. Kapitonov VV, Jurka J. 2006. Self-synthesizing DNA transposons in eukaryotes. Proc Natl Acad Sci U S A 103:4540–4545. https://doi.org/10.1073/pnas.0600833103.
163. Pritham EJ, Putliwala T, Feschotte C. 2007. *Mavericks*, a novel class of giant transposable elements widespread in eukaryotes and related to DNA viruses. Gene 390:3–17. https://doi.org/10.1016/j.gene.2006.08.008.
164. Barreat JGN, Katzourakis A. 2021. Phylogenomics of the *Maverick* virus-like mobile genetic elements of vertebrates. Mol Biol Evol 38:1731–1743. https://doi.org/10.1093/molbev/msaa291.
165. Krupovic M, Bamford DH, Koonin EV. 2014. Conservation of major and minor jelly-roll capsid proteins in Polinton (Maverick) transposons suggests that they are bona fide viruses. Biol Direct 9:6. https://doi.org/10.1186/1745-6150-9-6.
166. Koonin EV, Krupovic M. 2017. Polintons, virophages and transpovirons: a tangled web linking viruses, transposons and immunity. Curr Opin Virol 25:7–15. https://doi.org/10.1016/j.coviro.2017.06.008.
167. Krupovic M, Koonin EV. 2016. Self-synthesizing transposons: unexpected key players in the evolution of viruses and defense systems. Curr Opin Microbiol 31:25–33. https://doi.org/10.1016/j.mib.2016.01.006.
168. Krupovic M, Koonin EV. 2015. Polintons: a hotbed of eukaryotic virus, transposon and plasmid evolution. Nat Rev Microbiol 13:105–115. https://doi.org/10.1038/nrmicro3389.
169. Yutin N, Shevchenko S, Kapitonov V, Krupovic M, Koonin EV. 2015. A novel group of diverse Polinton-like viruses discovered by metagenome analysis. BMC Biol 13:95. https://doi.org/10.1186/s12915-015-0207-4.
170. Bellas CM, Sommaruga R. 2021. Polinton-like viruses are abundant in aquatic ecosystems. Microbiome 9:13. https://doi.org/10.1186/s40168-020-00956-0.
171. Pagarete A, Grébert T, Stepanova O, Sandaa RA, Bratbak G. 2015. Tsv-N1: a novel DNA algal virus that infects *Tetraselmis striata*. Viruses 7:3937–3953. https://doi.org/10.3390/v7072806.
172. Desnues C, La Scola B, Yutin N, Fournous G, Robert C, Azza S, Jardot P, Monteil S, Campocasso A, Koonin EV, Raoult D. 2012. Provirophages and transpovirons as the diverse mobilome of giant viruses. Proc Natl Acad Sci U S A 109:18078–18083. https://doi.org/10.1073/pnas.1208835109.
173. Jeudy S, Bertaux L, Alempic JM, Lartigue A, Legendre M, Belmudes L, Santini S, Philippe N, Beucher L, Biondi EG, Juul S, Turner DJ, Couté Y, Claverie JM, Abergel C. 2020. Exploration of the propagation of transpovirons within *Mimiviridae* reveals a unique example of commensalism in the viral world. ISME J 14:727–739. https://doi.org/10.1038/s41396-019-0565-y.
174. Krupovic M, Yutin N, Koonin EV. 2016. Fusion of a superfamily 1 helicase and an inactivated DNA polymerase is a signature of common evolutionary history of polintons, polinton-like viruses, Tlr1 transposons and transpovirons. Virus Evol 2:vew019. https://doi.org/10.1093/ve/vew019.
175. Ptashne M. 2004. A genetic switch: phage lambda revisited, 3rd ed. Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY.
176. Benler S, Koonin EV. 2020. Phage lysis-lysogeny switches and programmed cell death: Danse macabre. Bioessays 42:e2000114. https://doi.org/10.1002/bies.202000114.
177. Mizuuchi M, Mizuuchi K. 1989. Efficient Mu transposition requires interaction of transposase with a DNA sequence at the Mu operator: implications for regulation. Cell 58:399–408. https://doi.org/10.1016/0092-8674(89)90854-4.
178. Montaño SP, Pigli YZ, Rice PA. 2012. The μ transpososome structure sheds light on DDE recombinase evolution. Nature 491:413–417. https://doi.org/10.1038/nature11602.
179. Morissette G, Flamand L. 2010. Herpesviruses and chromosomal integration. J Virol 84:12100–12109. https://doi.org/10.1128/JVI.01169-10.
180. Flamand L. 2018. Chromosomal integration by human herpesviruses 6A and 6B. Adv Exp Med Biol 1045:209–226. https://doi.org/10.1007/978-981-10-7230-7_10.
181. Inoue Y, Saga T, Aikawa T, Kumagai M, Shimada A, Kawaguchi Y, Naruse K, Morishita S, Koga A, Takeda H. 2017. Complete fusion of a transposon

and herpesvirus created the *Teratorn* mobile element in medaka fish. Nat Commun 8:551. https://doi.org/10.1038/s41467-017-00527-2.
182. Koonin EV, Krupovic M. 2018. The depths of virus exaptation. Curr Opin Virol 31:1–8. https://doi.org/10.1016/j.coviro.2018.07.011.
183. Ghequire MGK, De Mot R. 2015. The tailocin tale: peeling off phage tails. Trends Microbiol 23:587–590. https://doi.org/10.1016/j.tim.2015.07.011.
184. Taylor NMI, van Raaij MJ, Leiman PG. 2018. Contractile injection systems of bacteriophages and related systems. Mol Microbiol 108:6–15. https://doi.org/10.1111/mmi.13921.
185. Patz S, Becker Y, Richert-Pöggeler KR, Berger B, Ruppel S, Huson DH, Becker M. 2019. Phage tail-like particles are versatile bacterial nanomachines - a mini-review. J Adv Res 19:75–84. https://doi.org/10.1016/j.jare.2019.04.003.
186. Wang F, Baquero DP, Beltran LC, Su Z, Osinski T, Zheng W, Prangishvili D, Krupovic M, Egelman EH. 2020. Structures of filamentous viruses infecting hyperthermophilic archaea explain DNA stabilization in extreme environments. Proc Natl Acad Sci U S A 117:19643–19652. https://doi.org/10.1073/pnas.2011125117.
187. Wang F, Baquero DP, Su Z, Osinski T, Prangishvili D, Egelman EH, Krupovic M. 2020. Structure of a filamentous virus uncovers familial ties within the archaeal virosphere. Virus Evol 6:veaa023. https://doi.org/10.1093/ve/veaa023.
188. Liu Y, Osinski T, Wang F, Krupovic M, Schouten S, Kasson P, Prangishvili D, Egelman EH. 2018. Structural conservation in a membrane-enveloped filamentous virus infecting a hyperthermophilic acidophile. Nat Commun 9:3360. https://doi.org/10.1038/s41467-018-05684-6.
189. Kasson P, DiMaio F, Yu X, Lucas-Staat S, Krupovic M, Schouten S, Prangishvili D, Egelman EH. 2017. Model for a novel membrane envelope in a filamentous hyperthermophilic virus. Elife 6:e26268. https://doi.org/10.7554/eLife.26268.
190. DiMaio F, Yu X, Rensen E, Krupovic M, Prangishvili D, Egelman EH. 2015. A virus that infects a hyperthermophile encapsidates A-form DNA. Science 348:914–917. https://doi.org/10.1126/science.aaa4181.
191. Baquero DP, Liu Y, Wang F, Egelman EH, Prangishvili D, Krupovic M. 2020. Structure and assembly of archaeal viruses, p 127–164. *In* Kielian M, Mettenleiter TC, Roossinck MJ (ed), Advances in virus research, vol 108. Virus assembly and exit pathways. Academic Press, Cambridge, MA. https://doi.org/10.1016/bs.aivir.2020.09.004.
192. Iranzo J, Koonin EV, Prangishvili D, Krupovic M. 2016. Bipartite network analysis of the archaeal virosphere: evolutionary connections between viruses and capsidless mobile elements. J Virol 90:11043–11055. https://doi.org/10.1128/JVI.01622-16.
193. Wille M, Netter HJ, Littlejohn M, Yuen L, Shi M, Eden J-S, Klaassen M, Holmes EC, Hurt AC. 2018. A divergent hepatitis D-like agent in birds. Viruses 10:720. https://doi.org/10.3390/v10120720.
194. Chang W-S, Pettersson JH-O, Le Lay C, Shi M, Lo N, Wille M, Eden J-S, Holmes EC. 2019. Novel hepatitis D-like agents in vertebrates and invertebrates. Virus Evol 5:vez021. https://doi.org/10.1093/ve/vez021.
195. Paraskevopoulou S, Pirzer F, Goldmann N, Schmid J, Corman VM, Gottula LT, Schroeder S, Rasche A, Muth D, Drexler JF, Heni AC, Eibner GJ, Page RA, Jones TC, Müller MA, Sommer S, Glebe D, Drosten C. 2020. Mammalian deltavirus without hepadnavirus coinfection in the neotropical rodent *Proechimys semispinosus*. Proc Natl Acad Sci U S A 117:17977–17983. https://doi.org/10.1073/pnas.2006750117.
196. Bergner LM, Orton RJ, Broos A, Tello C, Becker DJ, Carrera JE, Patel AH, Biek R, Streicker DG. 2021. Diversification of mammalian deltaviruses by host shifting. Proc Natl Acad Sci U S A 118:e2019907118. https://doi.org/10.1073/pnas.2019907118.
197. Iwamoto M, Shibata Y, Kawasaki J, Kojima S, Li YT, Iwami S, Muramatsu M, Wu H-L, Wada K, Tomonaga K, Watashi K, Horie M. 2021. Identification of novel avian and mammalian deltaviruses provides new insights into deltavirus evolution. Virus Evol 7:veab003. https://doi.org/10.1093/ve/veab003.
198. de la Peña M, Ceprián R, Casey JL, Cervera A. 2021. Hepatitis delta virus-like circular RNAs from diverse metazoans encode conserved hammerhead ribozymes. Virus Evol 7:veab016. https://doi.org/10.1093/ve/veab016.
199. Edgar RC, Taylor J, Lin V, Altman T, Barbera P, Meleshko D, Lohr D, Novakovsky G, Buchfink B, Al-Shayeb B, Banfield JF, de la Peña M, Korobeynikov A, Chikhi R, Babaian A. 14 March 2021. Petabase-scale sequence alignment catalyses viral discovery. bioRxiv https://doi.org/10.1101/2020.08.07.241729.
200. Wang HW, Chen PJ, Lee CZ, Wu HL, Chen DS. 1994. Packaging of hepatitis delta virus RNA via the RNA-binding domain of hepatitis delta antigens: different roles for the small and large delta antigens. J Virol 68:6363–6371. https://doi.org/10.1128/JVI.68.10.6363-6371.1994.
201. Wang C-C, Chang T-C, Lin C-W, Tsui H-L, Chu PBC, Chen B-S, Huang Z-S, Wu H-N. 2003. Nucleic acid binding properties of the nucleic acid chaperone domain of hepatitis delta antigen. Nucleic Acids Res 31:6481–6492. https://doi.org/10.1093/nar/gkg857.
202. Sureau C. 2006. The role of the HBV envelope proteins in the HDV replication cycle. Curr Top Microbiol Immunol 307:113–131. https://doi.org/10.1007/3-540-29802-9_6.
203. Perez-Vargas J, Amirache F, Boson B, Mialon C, Freitas N, Sureau C, Fusil F, Cosset F-L. 2019. Enveloped viruses distinct from HBV induce dissemination of hepatitis D virus *in vivo*. Nat Commun 10:2098. https://doi.org/10.1038/s41467-019-10117-z.
204. de la Peña M, Ceprián R, Cervera A. 2020. A singular and widespread group of mobile genetic elements: RNA circles with autocatalytic ribozymes. Cells 9:2555. https://doi.org/10.3390/cells9122555.
205. Goodrum G, Pelchat M. 2018. Insight into the contribution and disruption of host processes during HDV replication. Viruses 11:21. https://doi.org/10.3390/v11010021.
206. Flores R, Grubb D, Elleuch A, Nohales M-Á, Delgado S, Gago S. 2011. Rolling-circle replication of viroids, viroid-like satellite RNAs and hepatitis delta virus: variations on a theme. RNA Biol 8:200–206. https://doi.org/10.4161/rna.8.2.14238.
207. Flores R, Minoia S, Carbonell A, Gisel A, Delgado S, López-Carrasco A, Navarro B, Di Serio F. 2015. Viroids, the simplest RNA replicons: how they manipulate their hosts for being propagated and how their hosts react for containing the infection. Virus Res 209:136–145. https://doi.org/10.1016/j.virusres.2015.02.027.
208. Steger G, Riesner D. 2018. Viroid research and its significance for RNA technology and basic biochemistry. Nucleic Acids Res 46:10563–10576. https://doi.org/10.1093/nar/gky903.
209. Jimenez RM, Polanco JA, Lupták A. 2015. Chemistry and biology of self-cleaving ribozymes. Trends Biochem Sci 40:648–661. https://doi.org/10.1016/j.tibs.2015.09.001.
210. Wang Y. 2021. Current view and perspectives in viroid replication. Curr Opin Virol 47:32–37. https://doi.org/10.1016/j.coviro.2020.12.004.
211. Xie H, Sun H, Mu R, Li S, Li Y, Yang C, Xu M, Duan X, Chen L. 2021. The role of circular RNAs in viral infection and related diseases. Virus Res 291:198205. https://doi.org/10.1016/j.virusres.2020.198205.
212. Badar U, Venkataraman S, AbouHaidar M, Hefferon K. 2021. Molecular interactions of plant viral satellites. Virus Genes 57:1–22. https://doi.org/10.1007/s11262-020-01806-9.
213. Symons RH, Randles JW. 1999. Encapsidated circular viroid-like satellite RNAs (virusoids) of plants. Curr Top Microbiol Immunol 239:81–105. https://doi.org/10.1007/978-3-662-09796-0_5.
214. Shrestha N, Bujarski JJ. 2020. Long noncoding RNAs in plant viroids and viruses: a review. Pathogens 9:765. https://doi.org/10.3390/pathogens9090765.
215. AbouHaidar MG, Venkataraman S, Golshani A, Liu B, Ahmad T. 2014. Novel coding, translation, and gene expression of a replicating covalently closed circular RNA of 220 nt. Proc Natl Acad Sci U S A 111:14542–14547. https://doi.org/10.1073/pnas.1402814111.
216. Fiallo-Olivé E, Tovar R, Navas-Castillo J. 2016. Deciphering the biology of deltasatellites from the New World: maintenance by New World begomoviruses and whitefly transmission. New Phytol 212:680–692. https://doi.org/10.1111/nph.14071.
217. Zhou X. 2013. Advances in understanding begomovirus satellites. Annu Rev Phytopathol 51:357–381. https://doi.org/10.1146/annurev-phyto-082712-102234.
218. Hassan I, Orílio AF, Fiallo-Olivé E, Briddon RW, Navas-Castillo J. 2016. Infectivity, effects on helper viruses and whitefly transmission of the deltasatellites associated with sweepoviruses (genus *Begomovirus*, family *Geminiviridae*). Sci Rep 6:30204. https://doi.org/10.1038/srep30204.
219. Mubin M, Ijaz S, Nahid N, Hassan M, Younus A, Qazi J, Nawaz-Ul-Rehman MS. 2020. Journey of begomovirus betasatellite molecules: from satellites to indispensable partners. Virus Genes 56:16–26. https://doi.org/10.1007/s11262-019-01716-5.
220. Mansoor S, Zafar Y, Briddon RW. 2006. Geminivirus disease complexes: the threat is spreading. Trends Plant Sci 11:209–212. https://doi.org/10.1016/j.tplants.2006.03.003.
221. Arkhipova IR. 2017. Using bioinformatic and phylogenetic approaches to classify transposable elements and understand their complex evolutionary histories. Mob DNA 8:19. https://doi.org/10.1186/s13100-017-0103-2.

222. Toro N, Martínez-Abarca F. 2013. Comprehensive phylogenetic analysis of bacterial group II intron-encoded ORFs lacking the DNA endonuclease domain reveals new varieties. PLoS One 8:e55102. https://doi.org/10.1371/journal.pone.0055102.
223. Toro N, Nisa-Martínez R. 2014. Comprehensive phylogenetic analysis of bacterial reverse transcriptases. PLoS One 9:e114083. https://doi.org/10.1371/journal.pone.0114083.
224. Agrawal RK, Wang HW, Belfort M. 2016. Forks in the tracks: group II introns, spliceosomes, telomeres and beyond. RNA Biol 13:1218–1222. https://doi.org/10.1080/15476286.2016.1244595.
225. Krupovic M, Makarova KS, Forterre P, Prangishvili D, Koonin EV. 2014. Casposons: a new superfamily of self-synthesizing DNA transposons at the origin of prokaryotic CRISPR-Cas immunity. BMC Biol 12:36. https://doi.org/10.1186/1741-7007-12-36.
226. Krupovic M, Béguin P, Koonin EV. 2017. Casposons: mobile genetic elements that gave rise to the CRISPR-Cas adaptation machinery. Curr Opin Microbiol 38:36–43. https://doi.org/10.1016/j.mib.2017.04.004.
227. Yutin N, Bäckström D, Ettema TJG, Krupovic M, Koonin EV. 2018. Vast diversity of prokaryotic virus genomes encoding double jelly-roll major capsid proteins uncovered by genomic and metagenomic sequence analysis. Virol J 15:67. https://doi.org/10.1186/s12985-018-0974-y.
228. Christie GE, Dokland T. 2012. Pirates of the *Caudovirales*. Virology 434:210–221. https://doi.org/10.1016/j.virol.2012.10.028.
229. Mitarai N. 2020. How pirate phage interferes with helper phage: comparison of the two distinct strategies. J Theor Biol 486:110096. https://doi.org/10.1016/j.jtbi.2019.110096.
230. Dokland T. 2019. Molecular piracy: redirection of bacteriophage capsid assembly by mobile genetic elements. Viruses 11:1003. https://doi.org/10.3390/v11111003.
231. Martínez-Rubio R, Quiles-Puchalt N, Martí M, Humphrey S, Ram G, Smyth D, Chen J, Novick RP, Penadés JR. 2017. Phage-inducible islands in the Gram-positive cocci. ISME J 11:1029–1042. https://doi.org/10.1038/ismej.2016.163.
232. Penadés JR, Christie GE. 2015. The phage-inducible chromosomal islands: a family of highly evolved molecular parasites. Annu Rev Virol 2:181–201. https://doi.org/10.1146/annurev-virology-031413-085446.
233. Wang Y, Duan Z, Zhu H, Guo X, Wang Z, Zhou J, She Q, Huang L. 2007. A novel *Sulfolobus* non-conjugative extrachromosomal genetic element capable of integration into the host genome and spreading in the presence of a fusellovirus. Virology 363:124–133. https://doi.org/10.1016/j.virol.2007.01.035.
234. Arnold HP, She Q, Phan H, Stedman K, Prangishvili D, Holz I, Kristjansson JK, Garrett R, Zillig W. 1999. The genetic element pSSVx of the extremely thermophilic crenarchaeon *Sulfolobus* is a hybrid between a plasmid and a virus. Mol Microbiol 34:217–226. https://doi.org/10.1046/j.1365-2958.1999.01573.x.
235. Pfeifer E, Moura de Sousa JA, Touchon M, Rocha EPC. 2021. Bacteria have numerous distinctive groups of phage-plasmids with conserved phage and variable plasmid gene repertoires. Nucleic Acids Res 49:2655–2673. https://doi.org/10.1093/nar/gkab064.
236. Krupovic M, Gonnet M, Hania WB, Forterre P, Erauso G. 2013. Insights into dynamics of mobile genetic elements in hyperthermophilic environments from five new *Thermococcus* plasmids. PLoS One 8:e49044. https://doi.org/10.1371/journal.pone.0049044.
237. Gauthier J, Drezen JM, Herniou EA. 2018. The recurrent domestication of viruses: major evolutionary transitions in parasitic wasps. Parasitology 145:713–723. https://doi.org/10.1017/S0031182017000725.
238. Strand MR, Burke GR. 2020. Polydnaviruses: evolution and function. Curr Issues Mol Biol 34:163–182. https://doi.org/10.21775/cimb.034.163.
239. Darboux I, Cusson M, Volkoff AN. 2019. The dual life of ichnoviruses. Curr Opin Insect Sci 32:47–53. https://doi.org/10.1016/j.cois.2018.10.007.
240. Thézé J, Bézier A, Periquet G, Drezen JM, Herniou EA. 2011. Paleozoic origin of insect large dsDNA viruses. Proc Natl Acad Sci U S A 108:15931–15935. https://doi.org/10.1073/pnas.1105580108.
241. Strand MR, Burke GR. 2013. Polydnavirus-wasp associations: evolution, genome organization, and function. Curr Opin Virol 3:587–594. https://doi.org/10.1016/j.coviro.2013.06.004.
242. Nichols RJ, Cassidy-Amstutz C, Chaijarasphong T, Savage DF. 2017. Encapsulins: molecular biology of the shell. Crit Rev Biochem Mol Biol 52:583–594. https://doi.org/10.1080/10409238.2017.1337709.
243. Giessen TW, Silver PA. 2017. Widespread distribution of encapsulin nanocompartments reveals functional diversity. Nat Microbiol 2:17029. https://doi.org/10.1038/nmicrobiol.2017.29.
244. Kaneko-Ishino T, Ishino F. 2012. The role of genes domesticated from LTR retrotransposons and retroviruses in mammals. Front Microbiol 3:262. https://doi.org/10.3389/fmicb.2012.00262.
245. Ueda MT, Kryukov K, Mitsuhashi S, Mitsuhashi H, Imanishi T, Nakagawa S. 2020. Comprehensive genomic analysis reveals dynamic evolution of endogenous retroviruses that code for retroviral-like protein domains. Mob DNA 11:29. https://doi.org/10.1186/s13100-020-00224-w.
246. Hantak MP, Einstein J, Kearns RB, Shepherd JD. 2021. Intercellular communication in the nervous system goes viral. Trends Neurosci 44:248–259. https://doi.org/10.1016/j.tins.2020.12.003.
247. Krupovic M, Dolja VV, Koonin EV. 2019. Origin of viruses: primordial replicators recruiting capsids from hosts. Nat Rev Microbiol 17:449–458. https://doi.org/10.1038/s41579-019-0205-6.
248. Krupovic M, Dolja VV, Koonin EV. 2020. The LUCA and its complex virome. Nat Rev Microbiol 18:661–670. https://doi.org/10.1038/s41579-020-0408-x.
249. Spang A, Ettema TJ. 2016. Microbial diversity: the tree of life comes of age. Nat Microbiol 1:16056. https://doi.org/10.1038/nmicrobiol.2016.56.
250. Bamford DH. 2003. Do viruses form lineages across different domains of life? Res Microbiol 154:231–236. https://doi.org/10.1016/S0923-2508(03)00065-2.
251. Vetten HJ, Haenni A-L. 2006. Taxon-specific suffixes for vernacular names. Arch Virol 151:1249–1250. https://doi.org/10.1007/s00705-006-0743-x.



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