ANNUAL REVIEWS

Annual Review of Virology

Symbiosis: Viruses as Intimate Partners

Marilyn J. Roossinck and Edelio R. Bazán

Center for Infectious Disease Dynamics, Department of Plant Pathology and Environmental Microbiology, Pennsylvania State University, University Park, Pennsylvania 16802; email: mjr25@psu.edu

Annu. Rev. Virol. 2017. 4:123–39

First published as a Review in Advance on August 8, 2017

The *Annual Review of Virology* is online at virology.annualreviews.org

https://doi.org/10.1146/annurev-virology-110615-042323

Keywords

virus ecology, beneficial viruses, arms race, virus-host interactions

Abstract

Viruses must establish an intimate relationship with their hosts and vectors in order to infect, replicate, and disseminate; hence, viruses can be considered as symbionts with their hosts. Symbiotic relationships encompass different lifestyles, including antagonistic (or pathogenic, the most well-studied lifestyle for viruses), commensal (probably the most common lifestyle), and mutualistic (important beneficial partners). Symbiotic relationships can shape the evolution of the partners in a holobiont, and placing viruses in this context provides an important framework for understanding virus-host relationships and virus ecology. Although antagonistic relationships are thought to lead to coevolution, this is not always clear in virus-host interactions, and impacts on evolution may be complex. Commensalism implies a hitchhiking role for viruses—selfish elements just along for the ride. Mutualistic relationships have been described in detail in the past decade, and they reveal how important viruses are in considering host ecology. Ultimately, symbiosis can lead to symbiogenesis, or speciation through fusion, and the presence of large amounts of viral sequence in the genomes of everything from bacteria to humans, including some important functional genes, illustrates the significance of viral symbiogenesis in the evolution of all life on Earth.

INTRODUCTION

Symbiosis is a concept fraught with misunderstanding, and the literature is full of various definitions. Here we use the original definition of symbiosis as described by Frank and de Bary in the nineteenth century from their studies on lichen. The two critical aspects of this definition are that the entities must be in an intimate relationship, living in or on one another, and that the entities must be dissimilar (1). Symbiotic relationships are not necessarily beneficial; antagonistic symbioses also are common, and for viruses, commensal relationships, where there is no observable cost to the host, are probably the most common. Symbiotic relationships fall on a continuum between mutualistic and antagonistic, where the environment affects the placement of the holobiont on the continuum, a relationship known as conditional mutualism (**Figure 1**) (2, 3). Although some definitions of symbiosis use the term parasitism instead of antagonism, this further muddies the waters; all viruses, and indeed many other symbiotic microbes, are parasitic, meaning they benefit from their hosts by acquiring nutrients from them. This does not mean that they cannot also be commensal or mutualistic; these distinctions depend on whether or not the benefits outweigh the costs. Finally, mutualism does not necessarily imply symbiosis. For example, just because humans eat fruit and thus are involved in seed distribution, humans and fruiting plants do not live in an intimate relationship (in or on one another), and hence, even though the relationships are mutualistic, they are not symbiotic.

Symbiotic relationships are ubiquitous, spanning all domains of life, and vary in complexity and size from the two-entity fungus-algae codependence in lichen to the diverse microbial dynamics in biofilm formation. Most symbiotic relationships in nature involve multiple entities, but there is a dearth of information about these types of relationships because of the difficulty in studying them (4). Symbiotic interactions can vary temporally and may transition from one end of the mutualism–antagonism spectrum to the other (**Figure 2**) (5). Considering viruses as symbionts provides a framework for understanding the role of viruses in the interdependence of life. Although viruses have traditionally been discussed as symbionts by virologists, the field of symbiosis also embraced the inclusion of viruses in 2007 (6).

Viruses are the most abundant and diverse biological entities on the planet. Recent biodiversity surveys in desert, ocean, soil, mammalian gut, and plant ecosystems have uncovered an abundance of viruses in every ecosystem and life form examined (7–12). These ecological surveys also highlight a common misconception about virus biology: In spite of their ubiquitous incidence, most viruses produce no recognizable symptoms associated with disease (11, 13–15). Interactions among viruses and their respective hosts are dynamic and variable and constitute important forces shaping populations.

By definition, viruses are obligate intracellular parasites, and most studies of viruses have concentrated on describing their association with disease(s). Since the discovery of viruses as filterable infectious agents in plants (16), scientific inquiry exploring them has emphasized their role as pathogens, eclipsing their ecological roles in the symbiosis continuum of life (**Figure 2**). Viruses are often seen as strictly antagonistic, and their presence is usually considered detrimental to the host; however, work within the past two decades has elucidated the dynamic roles of viruses in land and ocean biogeochemical cycles and ecology (7–10), and a number of examples of mutualistic relationships between viruses and their hosts have been uncovered (17).

Due to their evolutionary plasticity, viruses are excellent models for understanding the formation and maintenance of symbiotic relationships. In this review, we discuss the various roles played by viruses as symbiotic partners with their hosts, from antagonistic to mutualistic associations.

An important aspect of symbiosis is that it can lead to symbiogenesis, or the evolution of new species through fusion. Although recognized in the evolution of *Eukaryota*, symbiogenesis is still largely thought to be a rare and odd event (18). However, it has been an important driving factor

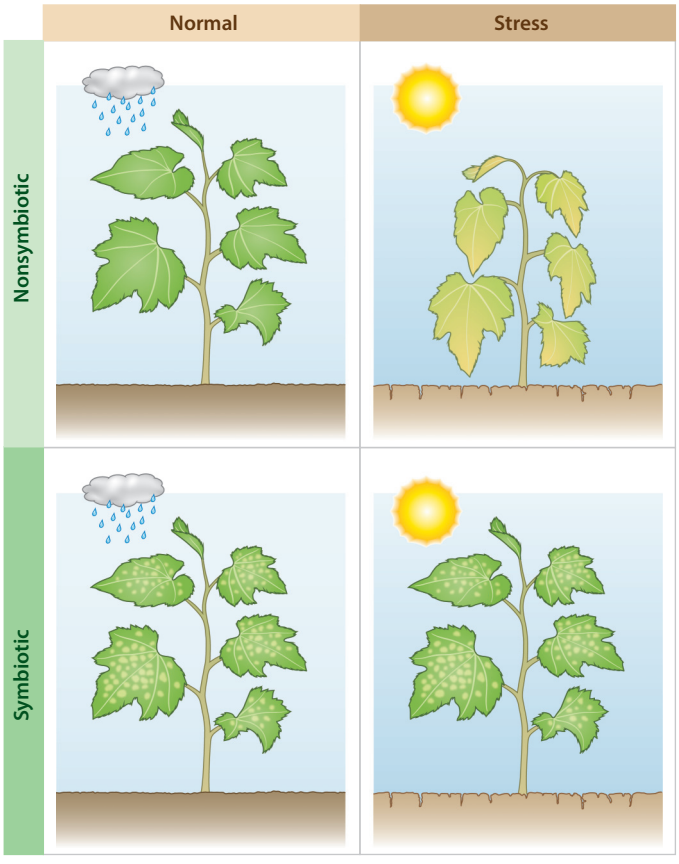

Figure 1

Conditional mutualism. In plants, infection with many acute viruses confers drought tolerance. If there is adequate rainfall, the virus-plant symbiosis is antagonistic, but under dry conditions, the relationship switches to mutualistic.

in virus evolution, as evidenced by the modular nature of viral genomes (19). In addition, the overwhelming abundance of viral sequences in extant genomes (20, 21) is evidence of the critical role of viral symbiogenesis in the evolution of life (22), discussed in the final section of this review. We view viruses as important ecological drivers of trait and genetic diversity in the holobiont, defined as the total of an organism and all of its associated microbes (23).

ANTAGONISTIC SYMBIOSIS—VIRUSES AND HOSTS IN CONFLICT

Since its inception, virology has focused on viruses as causative agents of disease and death in their hosts. This view is not surprising, as devastating epidemics have been observed across cellular life, although most studies have focused on diseases of humans and their domesticated plants and animals. Hence, most of the viruses discussed in the literature are antagonists—that is, they have a detrimental effect on their hosts that outweighs any benefits. Considering antagonistic relationships in the context of symbiosis provides a framework for understanding how they can shape the evolution of their hosts. The evolutionary arms race between viruses and their hosts is an often-invoked example of the outcome of antagonistic symbiosis (24). However, given the

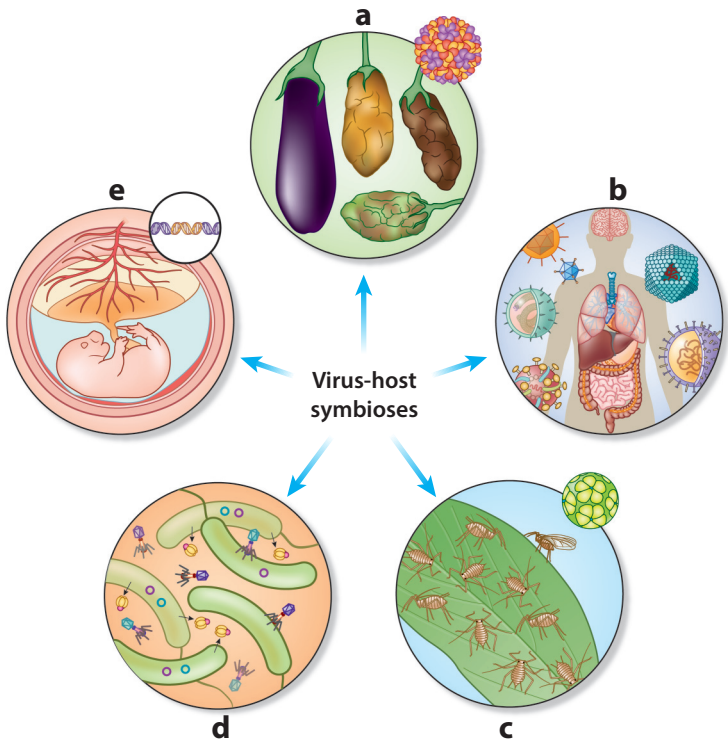

Figure 2

The spectrum of virus-host symbioses. Virus-host symbioses can range from (*a*) antagonistic, as in eggplant fruits infected with tomato bushy stunt virus; to (*b*) commensal, as in the numerous viruses found in and on humans that do not have any apparent impact on their hosts; to (*c*) conditionally mutualistic, as seen in the rosy apple aphid, where a virus induces the formation of the winged morph, smaller and less fecund but able to move to a new plant when crowding occurs; to (*d*) mutualistic, as seen in the infection of *Vibrio cholerae* by phages TCPφ and CTXφ, which carry genes for the toxin that allows invasion of the host gut; to (*e*) symbiogenic, as in the expression of an endogenous retrovirus *env* gene in mammals, which allows the formation of the placenta.

enormous evolutionary plasticity of viruses and the dramatic difference in generation times between viruses and their hosts, it is difficult to envision a straightforward coevolution where one entity changes in response to its partner in an ongoing competitive battle. The role of antagonistic viruses in shaping the evolution of their hosts is much more complex, and experimental studies are difficult. For example, the plant adaptive immune system that combats viruses, RNA silencing via small RNAs, is also involved in many aspects of gene regulation in development, control of transposon expression, formation of heterochromatin, and gene stability in plants and other organisms (25–27). Did viruses drive the evolution of this system that has such wide-spectrum influence, or did the host co-opt this already established system as a way to combat antagonistic viruses? Interferon—a master regulator of the immune system and cell metabolism that undoubtedly has other roles in mammalian physiology given that receptors are found on nearly all cell types—also responds to virus infection (28, 29), but did viruses drive the evolution of this system?

Coevolution has been thoroughly treated in the theoretical literature and is thought to have played a major role in the diversification of life on Earth (30). However, in the context of viruses

and their hosts, many questions remain about how coevolution can occur between a parasite and a host with dramatically different evolutionary dynamics: namely, much shorter generation times and lower replication fidelity in viruses compared with their hosts. There are generally two models for virus-host coevolution. The first is the arms race, in which the host develops resistance and the virus follows by increasing its infectivity. The second is fluctuating selection dynamics, in which the population of the host increases until a lethal virus takes over, whereupon the population of the host crashes and the virus population increases, in a cyclic manner. The outcome of the arms race is directional evolution of increasing resistance and increasing infectivity, whereas fluctuating selection results in the Red Queen effect, where evolution is not directional (31, 32). In marine virus–bacterial systems, however, viruses and hosts might maintain a different dynamic, where viruses infect different populations at different times, preventing the development of resistance and resulting in very high levels of genetic diversity in the host (33). Experimental coevolutionary studies with viruses are difficult and rare, but they have been most successful when using bacteria and their phages—although even in these systems, where generation times are very short, there has been little strong evidence to support any type of coevolution. In addition, a very narrow range of bacteria and viruses have been studied in laboratory settings, making generalization to the wider world difficult (reviewed in 34). However, in marine systems, the role of antagonistic viruses appears to in fact drive diversity of plankton (32, 35).

In the 1990s, the observation that some phages that could kill their hosts' competitors while simultaneously providing protection to their hosts led to the addiction model of virus-host interactions (36, 37). In this model, the antagonistic symbiosis between a bacterium and a lytic virus is ameliorated by the virus-encoded production of protection against the lytic phage; hence, the bacterium is addicted to the virus. A similar scenario is found in the killer viruses of yeast (see below) (38). This model was recently proposed to explain the viruses of giant viruses, referred to as virophages, an example of virus-virus antagonistic symbiosis (39).

COMMENSAL VIRUSES—VIRUSES AND HOSTS GETTING ALONG

Early microscopy-focused sampling and more recent advances in high-throughput sequencing technologies have revealed viruses to be ubiquitous and abundant in all cellular life and environments (40). The application of high-throughput sequencing and metagenomics analyses, exploring virus diversity in humans and other vertebrates, plants, insects, and a variety of environmental samples, gives a glimpse into the undiscovered diversity of viruses (41–48). Despite the staggering number of viruses in any given environment, many host populations do not demonstrate signs of virus-induced mortality or even disease. In fact, even while we accumulate more and more sequence information, advancing toward understanding what all these viruses are doing in the context of their hosts' biology or the larger ecosystem is still largely elusive (49). It seems likely that the majority of viruses are in fact largely commensal—that is, they do not have detectable negative impacts on their hosts.

In plant virus biodiversity surveys, viruses were found in thousands of plants, but no disease symptoms were seen that could be correlated with virus presence, even though viruses closely related to crop pathogens were found (12, 44). Even in diseased individuals, many viruses cannot really be linked to disease. In metagenomic studies of the human gut using diarrhea samples, there was no evidence that many of the recovered viruses were involved in the illness. Other studies in the human virome also find many viruses but few links with disease (50, 51). The ubiquity, diversity, and abundance of viruses suggest the viral infectious agents are commonplace in all cellular life. In this light, viruses can be seen as impartial members of microbial communities, and pathology from virus infection could be viewed as atypical.

MUTUALISTIC VIRUSES—VIRUSES HELPING THEIR HOSTS

Recent reviews on beneficial viruses include hosts that span the spectrum from prokaryotes to fungi, insects, plants, and mammals (17, 52, 53). Bacteriophages encode toxins and other factors that facilitate the invasion of the bacterial macrohosts, and in fact, most bacterial pathogens of humans are enabled by their phages (54, 55). Phages are involved in the horizontal gene transfer of essential elements, either by direct methods, such as integration into host genomes (lysogeny) and transduction, or by indirect methods, such as transformation of DNA from lysed cellular debris (56, 57). Integration of temperate viruses could provide the bacterial host with many advantages over its noninfected counterparts, such as better resistance to environmental stressors (58, 59); new cellular functions, such as the acquisition of photosynthetic genes in cyanobacteria of the genera *Prochlorococcus* and *Synechococcus* (60); a source of protection from other viruses through superinfection exclusion (61, 62); and modulation of host metabolism through expression of auxiliary metabolic genes, genes that are not involved in virus replication and function but that modify host metabolic processes that favor virus replication (63). Phages may be very important in the production of bacterial biofilms (64, 65). In very dense viral populations, viruses could function as a reservoir of nutrients. For example, in nutrient-poor environments such as coral reefs, viruses are captured and digested by marine sponges (66).

Bacteria can harbor viruses that kill their competitors while largely protecting their hosts, helping them invade new territories. This can be done through toxins that kill competitors, or by conversion of a few members of the population to a lytic state, producing viruses that kill nonlysogenic competitors (67, 68). In these competitive interactions, the viruses and their gene products are used to combat competition through the release of toxins such as bacteriocins. In large populations of *Salmonella enterica*, competition can be eliminated by having members of the population release toxins in a phage-induced manner; additionally, *S. enterica* harboring lysogenic phage are protected from bacteriocin toxin (69). These phage-induced secretions can be considered public goods. The virus may directly provide benefits to the bacterial population by eliminating competition, or may increase the availability of nutrients and extracellular genetic material by lysing neighboring bacteria (68).

Viruses of eukaryotic microbes enhance the growth, fecundity, and persistence of their hosts within the macrohost (70). For example, in leishmaniasis, caused by species of the microbial parasite genus *Leishmania*, host invasion in humans and other mammals is enhanced by the presence of *Leishmaniavirus*, which suppresses aspects of the host immune response (71). *Trichomonas vaginalis* viruses also may be involved in allowing the parasite to evade the host immune system (72, 73). The killer virus in yeast provides a fascinating system of protection for the host. The virus produces a toxin in an inactive form that is released into the environment and readily taken up by other yeast. The activation of the toxin occurs by processing after uptake. However, in yeast harboring the virus, the presence of the inactive toxin already in the cell moves all forms of the toxin into the ubiquitin degradation pathway, preventing the killer effect (38).

In plants, viruses can ameliorate the impacts of biotic stress; for example, white clover plants are less attractive to fungal gnats when they are infected with white clover mosaic virus (74), and wild gourds are less attractive to beetles when they are infected with zucchini yellow mosaic virus (75). Viruses can also help plants with abiotic stresses. All acute viruses tested conferred drought tolerance to plants, and cucumber mosaic virus also can confer cold tolerance (76). Virus-conferred drought tolerance also has been observed in field studies (77). The mechanism for drought tolerance imparted by cucumber mosaic virus was recently shown to involve RNA silencing (78), although other factors also may be involved. Elevated levels of various metabolites have been implicated as well (76).

More complex symbioses are involved in some plant abiotic stress tolerance. In Yellowstone National Park, plants that can survive in geothermal areas tolerate the high soil temperatures only when they are colonized by a fungus that is, in turn, infected with a virus (79). In white clover, a persistent plant virus, white clover cryptic virus, prevents the formation of nitrogen-fixing nodules (a process that is costly for the plants) if there is adequate nitrogen present in the soil (80).

Mutualistic viruses in insects have positive effects on development, life span, and fecundity, along with enhancing resistance to biocontrol methods (81). A densovirus that infects the rosy apple aphid induces the development of wings. This morphotype is important in moving aphids to new plants (82). Viruses that infect both plants and insects, such as tomato spotted wilt virus, can benefit their insect hosts at the expense of the plant host by making the plant a better host for the insects (83). This interaction can also benefit other insects, like spider mites (84).

Infection with GB virus C is asymptomatic in humans and could thus be considered a commensal virus, but under some conditions, it becomes a mutualist. Patients who are HIV positive show slower progression of disease when they are infected with GB virus C. Several effects on HIV, including downregulation of cell receptors for entry, reduced replication, effects on interferon synthesis, and interactions with interleukin pathways, have been seen in clinical studies and in vitro (85).

In germ-free mice, murine norovirus can replace gut bacteria in establishing the architecture of the gut that is involved in the innate immune responses, including lymphocyte functions (86). Other mammalian viruses can provide additional immune functions. Mouse gammaherpesvirus protects mice from the bacterial pathogens that cause bubonic plague (*Yersinia pestis*) and the foodborne disease listeriosis (*Listeria monocytogenes*) (87). Latent herpesviruses also can arm natural killer cells that are an important defense against many pathogens and against cancer, poising them for cytotoxic effects (88). In humans the herpes virus cytomegalovirus, a nearly ubiquitous latent virus, provides enhanced immune response to influenza, especially in young adults (89). Other herpesviruses may also increase the immune response to other pathogens (90).

SYMBIOGENESIS—ENDOGENIZED VIRUSES AND HOST BIOLOGY

Symbiogenesis, or speciation through fusion, can be considered the extreme of symbiosis. This term, as well as the term endosymbiosis, was first used to explain the organelles in eukaryotic cells that are of prokaryotic origin (the mitochondria and chloroplasts). In the context of viruses we use the term to refer to genetic fusion of all or part of a virus genome with its host genome, or with another virus. Symbiogenesis has been a major driving force in the evolution of extant virus species, as demonstrated by the modular nature of viral genes (19). Viruses become part of their host's genome through the process of endogenization. This occurs when viral DNA integrates into host germ-line cells, which can then be inherited vertically in the population. Although the vast majority of endogenous virus elements (EVEs) are retroviral in origin (i.e., they are endogenous retroviruses, or ERVs), many nonretroviruses, including cytoplasmic RNA viruses, have been found in genomes as well (21). With the advancement of sequencing technologies and bioinformatics, EVEs have been discovered in virtually all genomes that have been analyzed, resulting in the relatively new field of paleovirology (91, 92). Because viruses do not a leave detectable fossil record, the EVEs are used as molecular fossils; once endogenized, their evolutionary rates become comparable to that of the host. EVEs can influence multiple facets of host biology, including

Table 1 Examples of endogenous retroviruses and endogenous viral elements with known functions

Endogenous viral element	Viral origin	Host	Role in host	Reference
syncytin	Retroviral *env*	Mammals	Formation of mammalian placenta	103
Endogenous Jaagsiekte sheep retrovirus	Betaretroviral *env*	Sheep	Receptor interference against similar viruses	105
Endogenous feline leukemia virus	Retroviral *env*	Cat	Receptor interference against similar viruses	105
Endogenous retroviral long terminal repeat	Retroviral long terminal repeat	Human	Expression of salivary amylase	111
gypsy	Retroviral *gag*, *pol*, *env*	Fruit fly	Competitive inhibition against vertically transmitted symbionts; can exogenize and infect new cells	128
Iris	Retroviral *env*	Fruit fly	Immunity to endogenous virus infection?	126
Grp	Retroviral *gag*	Fruit fly	May provide immunity to endogenous virus infection	127
Endogenous banana streak virus	*Caulimoviridae* pararetrovirus	Banana	Can exogenize and cause host death	118
Endogenous petunia vein clearing virus	Petuvirus	Petunia	Histone modification	122
Lyc endogenous pararetrovirus	Pararetrovirus	Tomato	Produces small interfering RNAs that may protect from similar virus infection	121
Endogenous bornavirus-like elements	*Mononegavirales*	Ground squirrel	Potentially inhibits related viruses in vivo	140
Tf1 long terminal repeat retrotransposon	Not known	Yeast	Upregulates stress resistance genes	146

immune responses, and can become domesticated, providing genes or regulatory elements for novel functionality (**Table 1**).

Polydnaviruses

A well-studied example of viruses in the process of becoming symbiogenic is the large double-stranded DNA viruses of parasitoid wasps in the family *Polydnaviridae*. The parasitoid wasps, free-living insects during their adult stage, reproduce by laying eggs on or within the bodies of their larval hosts (*Lepidoptera*, *Coleoptera*, *Hymenoptera*, and *Hemiptera* spp.) (93). The wasp progeny mature into adults by parasitically feeding on the arthropods, usually resulting in the eventual death of the host. Polydnaviruses comprise two genera, *Bracovirus* and *Ichnovirus*, and are associated with more than 50,000 species of parasitoid wasps in the *Braconidae* and *Ichneumonidae* families. The partnerships between polydnaviruses and parasitoid wasps are ancient, estimated to have been established ~100 million years ago (94). The viral genes for replication and structural components are found in the wasp genome. The virus replicates actively in the adult female wasp but packages wasp virulence genes needed to disable the parasitized host's immune system, preventing encapsulation that would otherwise eject the parasitic wasp egg (93, 95). The bracoviruses, which are found in the braconid wasps, are hypothesized to originate from an infectious nudivirus (96), but the ichnoviruses appear to originate from a different infectious virus (97). Hence, the evolution of this virus-wasp symbiogenesis probably occurred more than once.

Endogenous Retroviruses

At the beginning of the twenty-first century, analysis of the newly assembled human genome revealed that ~8% of the genetic material is from retroviral origins (98); analogous studies in other vertebrates estimate ERVs to constitute 4–10% of their genomes (99). Across vertebrate animals, ERVs are common and extremely diverse, with multiple integration events by members of various virus families at different time points, giving a glimpse into past encounters between retroviruses and their hosts (100). Once integrated, ERVs are subject to evolutionary forces such as genetic drift and may accumulate frameshifts and stop codons resulting in defective viral fragments scattered throughout the genome. Other ERVs, however, remain active and have been co-opted by their hosts. These endogenized viral fragments can serve as a large reservoir of *cis*-regulatory elements (e.g., promoters and transcriptional regulators) and as protein-coding regions adopted by the host (101). Some of these endogenization events introduced major evolutionary innovations that provide a selective advantage to the host.

In mammals, ERV envelope genes have maintained some of their functions, including fusogenicity, recognition of specific cell receptors, and immunosuppressive activity (102). The domestication of the endogenized *env* gene is the precursor of the *syncytin* gene in mammals, an important gene required in the formation of the placenta, an essential organ whose main function is to form a fetal-maternal interface that provides support for the developing embryo by mediating metabolic exchanges (102–104). Phylogenetic analysis shows that *syncitin* has been endogenized and domesticated at least four times across different mammalian lineages. Some postulate that placentation arose once in the mammalian common ancestor by the capture of the founding retroviral *env* gene but since then has been replaced by subsequent *env* endogenization events during mammalian evolution and diversification (103, 104). The *env* replacement model helps explain the diversity of distinct *syncytin* genes and placental structures found in mammals, and the dating of *syncytin* across mammals ranges from 5 to 80 million years ago, with estimates dating the primitive placenta to about 150 million years ago (102).

ERVs have been implicated in structuring host immune responses. Examples of ERV-derived immunity have been documented in multiple eukaryotic lineages, and the number and diversity of known ERVs are expected to grow as genomic surveys become more available. These ERVs function as direct inhibitors of their contemporary viral counterparts (105). By co-opting and expressing receptor-binding genes (e.g., retroviral *env*), the host can saturate viral entry receptors and block infection; this has been documented in sheep protected against Jaagsiekte sheep retrovirus, mice protected against murine leukemia virus, and cats protected against feline leukemia virus (105, 106). These examples support the plague culling hypothesis that views the numerous ERVs to represent survivors of culling by waves of lethal retroviral plagues (107). Most of the ERVs in mammals are very ancient, but in koalas an endogenization process has been occurring over the past century, providing a unique opportunity for studying the process and effects of endogenization (108).

Retroviral long terminal repeats (LTRs) function as promoters and enhancers that normally regulate viral expression and transcription. Once integrated, any of these LTR functions can disrupt local gene expression, resulting in a range of consequences for the host (109). Although mammalian cells have evolved epigenetic mechanisms to suppress LTR functions (110), there are still numerous cases where expression of genes is controlled by ERV-derived LTRs. One of the earliest-described examples is the expression of the starch-digesting enzyme amylase in human saliva that results from the insertion of an ERV-provided promoter (111), although the full importance of salivary amylase is not clear. ERV-derived LTRs are also implicated in the expression of long noncoding RNAs (112), whose roles in cell differentiation and development

appear to be extensive and are still being unraveled (113). Not all ERV-activated expression is positive. Numerous forms of cancer are linked to oncogene activation by ERVs (114), including adenocarcinoma (115) and some Hodgkin's lymphoma (116). ERVs have also been implicated in autoimmune diseases (117).

ERV-like elements are also found in plants and insects, and even in fungi. In plants, numerous endogenous pararetroviruses (EPRVs) are found in sequenced genomes, and some can be activated and cause episomal infections, where the viruses exogenize and establish acute infections (118, 119). In rice, EPRVs have been used for paleovirology studies similar to what has been done with other EVEs (120). EPRVs can affect their hosts in positive ways, such as by suppressing related viruses and enhancing the plant adaptive immune response, as seen in tomato with *Lyc*EPRV (121). In petunia, an EPRV affects histone modifications (122).

All eukaryotic genomes contain numerous transposable elements, making up as much as 80% of a given genome (123). These elements fall into a variety of categories, and those that are LTRs are most likely derived from ancient viruses, although arguably others may be remnants of viruses as well. LTRs are found in abundance in many eukaryotes, including invertebrates, and in a few cases they can be active viruses. For example, the *gypsy* element of *Drosophila melanogaster* can exogenize and infect oocytes (124) and competes with *Wolbachia* bacteria for maternal-offspring transmission (125). The endogenous *env* gene of *gypsy*, *Iris*, is under positive selection and may provide protection from exogenous retroviruses (126). Another element in *D. melanogaster*, *Grp*, thought to be the *gag* gene of a *gypsy* element, is expressed in an age- and gender-specific manner in the insects and also may provide protection (127). The insect ERVs have provided a rich resource for understanding the endogenization process (128).

Retroelements are also common in fungi (129, 130), and in the yeast *Schizosaccharomyces pombe* Tf1, an LTR retrotransposon inserts into the promoters of stress-response genes and may confer resistance to environmental stress (131).

Nonretroviral Endogenous Virus Elements

A surprising finding from the recent availability of genomic sequences is that many nonretroviruses are also found integrated into the genomes of just about everything. An early demonstration of a nonretroviral EVE was in plants, where geminivirus sequences were found integrated into several *Nicotiana* species (132). Perhaps even more surprising was the finding of sequence integration of a cytoplasmic RNA virus, a flavivirus, in mosquitoes (133). Since these early discoveries, numerous examples of nonretroviral EVEs have been described in many eukaryotic hosts, including mammals, insects, plants, and fungi (20, 134–136). As with ERVs, many of these appear to represent ancient events (134). For example, phylogenetic analysis of small circular DNA viral EVEs in vertebrates put their integration time at about 50 million years ago (137), and similar studies with RNA-based bornavirus-like EVEs and marburgvirus/ebolavirus-like EVEs put integration times at about 35 million years ago (138). Many of these elements have multiple integration sites, and some produce transcripts. The bornavirus-like EVEs also have been found in insect genomes (139). The initial study noted that integrated sequences were not found in animals where bornaviruses cause significant disease (138), and bornavirus-like EVEs were recently shown to inhibit virus replication (140), suggesting that nonretroviral EVEs may provide immunity just as some of their ERV counterparts do.

A number of double-stranded RNAs have been found in the genomes of plants and fungi, including sequences from members of the *Partitiviridae*, *Totiviridae*, and *Chrysoviridae* families (135, 136, 141). Estimations for integration times for partitivirus-like EVEs are about 10 million

years ago. Interestingly, although cytoplasmic partitivirus infections are widespread in both plants and fungi, and are generally thought to be benign or even beneficial, they have not been found in plants with integrated partitivirus-like EVEs (142). If they do provide a beneficial function for their plant hosts, it is possible that the beneficial genes have been moved into the plant genome in some cases, removing the need for the cytoplasmic virus. Negative-sense single-stranded RNA viruses in the family *Rhabdoviridae* are also found as EVEs in plants (136), and EVEs from a few positive-sense single-stranded RNA viruses have also been reported (141).

Other examples of genomes containing EVEs include those of crustaceans, where members of *Bunyaviridae*, *Circoviridae*, and *Parvoviridae*, as well as an unclassified member of *Mononegavirales*, are widespread (143). In most cases, functions of these EVEs are unknown; in yeast, EVEs derived from members of *Totiviridae* appear to be under positive selection and maintain intact open reading frames, although only a few are transcribed (144). Insect genomes also contain a large number of viruses in a variety of families, including double-stranded DNA viruses, double-stranded RNA viruses, and single-stranded RNA viruses (145).

It is clear that the endogenization of viral elements has sculpted the evolution of extant genomes in all domains of life (40). With new tools and more and more genomes available, it seems certain that the number of known symbiogenic viruses will grow, and more functions will undoubtedly be attributed to these ancient components of genomes.

CONCLUSIONS

Viruses have long been considered as existing on the fringe of life, and causing nothing but trouble for their hosts. By taking a different approach to virology, using the well-developed tenets of symbiosis, we can see that they are, in fact, central to life. Antagonistic viruses have been important in the development of many aspects of the immune response, population control, and overall ecology. Although most viruses appear to be commensal, these viruses may be poised to provide beneficial functions and add to the repertoire of genetic material available to their hosts when rapid changes are necessary. Mutualistic viruses have been described across all kingdoms of life and play central roles in the health or survival of their hosts. Symbiogenic viruses make up large portions of modern genomes and can provide novel materials for genetic innovation. Without our viruses, where would we be?

DISCLOSURE STATEMENT

The authors are not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review.

ACKNOWLEDGMENTS

The authors acknowledge support from the Pennsylvania State University College of Agriculture and the Huck Institute for Life Sciences.

LITERATURE CITED

1. de Bary HA. 1879. *Die Erscheinung der Symbiose*. Strassburg, Ger.: Verlag von Karl J. Trübner
2. Rodriguez RJ, Henson J, Van Volkenburgh E, Hoy M, Wright L, et al. 2008. Stress tolerance in plants via habitat-adapted symbiosis. *ISME J.* 2:404–16
3. Bao X, Roossinck MJ. 2013. A life history view of mutualistic viral symbioses: quantity or quality for cooperation? *Curr. Opin. Microbiol.* 16:514–18

4. Hussa EA, Goodrich-Blair H. 2013. It takes a village: ecological and fitness impacts of multipartite mutualism. *Annu. Rev. Microbiol.* 67:161–78
5. Roossinck MJ. 2015. Plants, viruses and the environment: ecology and mutualism. *Virology* 479–80:271–77
6. Margulis L, Hall J, McFall-Ngai M. 2007. Our discipline comes of age. *Symbiosis* 44:ii–iv
7. Zablocki O, Ardriaenssens EM, Cowan D. 2016. Diversity and ecology of viruses in hyperarid desert soils. *Appl. Environ. Microbiol.* 82:770–77
8. Williamson KE, Radosevich M, Wommack KE. 2005. Abundance and diversity of viruses in six Delaware soils. *Appl. Environ. Microbiol.* 71:3119–25
9. Cowan DA, Makhalanyane TP, Dennis PG, Hopkins DW. 2014. Microbial ecology and biogeochemistry of continental Antarctic soils. *Front. Microbiol.* 5:154
10. Cadwell K. 2015. Expanding the role of the virome: commensalism in the gut. *J. Virol.* 89:1951–53
11. Breitbart M, Rohwer F. 2005. Here a virus, there a virus, everywhere the same virus? *Trends Microbiol.* 13:278–84
12. Roossinck MJ. 2012. Plant virus metagenomics: biodiversity and ecology. *Annu. Rev. Genet.* 46:357–67
13. Suttle CA. 2005. Viruses in the sea. *Nature* 437:356–61
14. Roossinck MJ. 2014. Metagenomics of plant and fungal viruses reveals an abundance of persistent lifestyles. *Front. Microbiol.* 5:767
15. Wren JD, Roossinck MJ, Nelson RS, Sheets K, Palmer MW, Melcher U. 2006. Plant virus biodiversity and ecology. *PLOS Biol.* 4:e80
16. Beijerinck MW. 1942 (1898). Concerning a contagium vivum fluidum as cause of the spot disease of tobacco leaves. *Phytopathol. Class.* 7:33–52
17. Roossinck MJ. 2015. Move over, bacteria! Viruses make their mark as mutualistic microbial symbionts. *J. Virol.* 89:1–3
18. Cavalier-Smith T. 2013. Symbiogenesis: mechanisms, evolutionary consequences, and systemic implications. *Annu. Rev. Ecol. Evol. Syst.* 44:145–72
19. Roossinck MJ. 2005. Symbiosis versus competition in the evolution of plant RNA viruses. *Nat. Rev. Microbiol.* 3:917–24
20. Aiewsakun P, Katzourakis A. 2015. Endogenous viruses: connecting recent and ancient viral evolution. *Virology* 479–80:26–37
21. Feschotte C, Gilbert C. 2012. Endogenous viruses: insights into viral evolution and impact on host biology. *Nat. Rev. Genet.* 13:283–96
22. Koonin EV. 2006. On the origin of cells and viruses: a comparative-genomic perspective. *Isr. J. Ecol. Evol.* 52:299–318
23. Guerrero R, Margulis L, Berlanga M. 2013. Symbiogenesis: the holobiont as a unit of evolution. *Int. Microbiol.* 16:133–43
24. Meyerson NR, Sawyer SL. 2011. Two-stepping through time: mammals and viruses. *Trends Microbiol.* 19:286–94
25. Chen X. 2012. Small RNAs in development—insights from plants. *Curr. Opin. Genet. Dev.* 22:361–67
26. Castel SE, Martienssen RA. 2013. RNA interference in the nucleus: roles for small RNAs in transcription, epigenetics and beyond. *Nat. Rev. Genet.* 14:100–12
27. Dunoyer P, Melnyk C, Molnar A, Slotkin RK. 2013. Plant mobile small RNAs. *Cold Spring Harb. Perspect. Biol.* 5:a017897
28. Hoffmann HH, Schneider WM, Rice CM. 2015. Interferons and viruses: an evolutionary arms race of molecular interactions. *Trends Immunol.* 36:124–38
29. Fritsch SD, Weichhart T. 2016. Effects of interferons and viruses on metabolism. *Front. Immunol.* 7:630
30. Hembry DH, Yoder JB, Goodman KR. 2014. Coevolution and the diversification of life. *Am. Nat.* 184: 425–38
31. Woolhouse MEJ, Webster JP, Domingo E, Charlesworth B, Levin BR. 2002. Biological and biomedical implications of the co-evolution of pathogens and their hosts. *Nat. Genet.* 32:569–77
32. Martiny JBH, Riemann L, Marston MF, Middelboe M. 2014. Antagonistic coevolution of marine planktonic viruses and their hosts. *Annu. Rev. Mar. Sci.* 6:391–414

33. Avrani S, Schwartz DA, Lindell D. 2012. Virus-host swinging party in the oceans. *Mob. Genet. Elem.* 2:88–95
34. Dennehy JJ. 2012. What can phages tell us about host-pathogen coevolution? *Int. J. Evol. Biol.* 2012:396165
35. Gustavsen JA, Winget DM, Tian X, Suttle CA. 2014. High temporal and spatial diversity in marine RNA viruses implies that they have an important role in mortality and structuring plankton communities. *Front. Microbiol.* 5:703
36. Lehnherr H, Maguin E, Jafri S, Yarmolinsky MB. 1993. Plasmid addition genes of bacteriophage P1: *doc*, which causes cell death on curing of prophage, and *phd*, which prevents host death when prophage is retained. *J. Mol. Biol.* 233:414–28
37. Engelberg-Kulka H, Glaser G. 1999. Addiction modules and programmed cell death and antideath in bacterial cultures. *Annu. Rev. Microbiol.* 53:43–70
38. Schmitt MJ, Breinig F. 2006. Yeast viral killer toxins: lethality and self-protection. *Nat. Rev. Microbiol.* 4:212–21
39. Villarreal LP. 2016. Persistent virus and addition modules: an engine of symbiosis. *Curr. Opin. Microbiol.* 31:70–79
40. Koonin EV, Dolja VV. 2013. A virocentric perspective on the evolution of life. *Curr. Opin. Virol.* 3:546–57
41. Reyes A, Blanton LV, Cao S, Zhao G, Manary M, et al. 2015. Gut DNA viromes of Malawian twins discordant for severe acute malnutrition. *PNAS* 112:11941–46
42. Reyes A, Haynes M, Hanson N, Angly FE, Heath AC, et al. 2010. Viruses in the faecal microbiota of monozygotic twins and their mothers. *Nature* 466:334–38
43. Holtz LR, Cao S, Zhao G, Bauer IK, Denno DM, et al. 2014. Geographic variation in the eukaryotic virome of human diarrhea. *Virology* 468–70:556–64
44. Roossinck MJ, Martin DP, Roumagnac P. 2015. Plant virus metagenomics: advances in virus discovery. *Phytopathology* 105:716–27
45. Simmonds P, Adams MJ, Benkő M, Breitbart M, Briste JR, et al. 2017. Consensus statement: virus taxonomy in the age of metagenomics. *Nat. Rev. Microbiol.* 15:161–68
46. Li C, Shi M, Tian J, Lin X, Kang Y, et al. 2015. Unprecedented genomic diversity of RNA viruses in arthropods reveals the ancestor of negative sense RNA viruses. *eLife* 4:e05378
47. Suttle CA. 2013. Viruses: unlocking the greatest biodiversity on Earth. *Genome* 56:542–44
48. Paez-Espino D, Eloe-Fadrosh EA, Pavlopoulos GA, Thomas AD, Huntemann M, et al. 2016. Uncovering Earth's virome. *Nature* 536:425–30
49. Wommack KE, Nasko DJ, Chopyk J, Sakowski EG. 2015. Counts and sequences, observations that continue to change our understanding of viruses in nature. *J. Microbiol.* 53:181–92
50. Lecuit M, Eloit M. 2013. The human virome: new tools and concepts. *Trends Microbiol.* 21:510–15
51. Lim ES, Zhou Y, Zhao G, Bauer IK, Droit L, et al. 2015. Early life dynamics of the human gut virome and bacterial microbiome in infants. *Nat. Med.* 21:1228–34
52. Roossinck MJ. 2011. The good viruses: viral mutualistic symbioses. *Nat. Rev. Microbiol.* 9:99–108
53. Virgin HW. 2014. The virome in mammalian physiology and disease. *Cell* 157:142–50
54. Donnenberg MS. 2000. Pathogenic strategies of enteric bacteria. *Nature* 406:768–74
55. Boyd EF. 2012. Bacteriphage-encoded bacterial virulence factors and phage-pathogenicity island interactions. *Adv. Virus Res.* 82:91–118
56. Keen EC, Bliskovsky VV, Malagon F, Baker JD, Prince JS, et al. 2017. Novel "superspreader" bacteriophages promote horizontal gene transfer by transformation. *mBio* 8:e02115-16
57. Gilbert C, Peccoud J, Chateigner A, Moumen B, Cordauz R, Herniou EA. 2016. Continuous influx of genetic material from host to virus populations. *PLOS Genet.* 12:e1005838
58. Lynch KH, Stothard P, Dennis JJ. 2010. Genomic analysis and relatedness of P2-like phages of the *Burkholderia cepacia* complex. *BMC Genom.* 11:599
59. Matos RC, Lapaque M, Rigottier-Gois L, Debarbieux L, Meylheuc T, et al. 2013. *Enterococcus faecalis* prophage dynamics and contributions to pathogenic traits. *PLOS Genet.* 9:6
60. Lindell D, Jaffe JD, Johnson ZI, Church GM, Chisholm SW. 2005. Photosynthesis genes in marine viruses yield proteins during host infection. *Nature* 438:86–89

61. Wang X, Kim Y, Ma Q, Hong SH, Polusaeva K, et al. 2010. Cryptic prophages help bacteria cope with adverse environments. *Nat. Commun.* 1:147
62. Sekulovic O, Fortier LC. 2015. Global transcriptional response of *Clostridium difficile* carrying the φCD38-2 prophage. *Appl. Environ. Microbiol.* 81:1364–74
63. Brum JR, Hurwitz BL, Schofield O, Ducklow HW, Sullivan MB. 2016. Seasonal time bombs: Dominant temperate viruses affect Sourthern Ocean microbial dynamics. *ISME J.* 10:437–49
64. Secor PR, Sweere JM, Michaels LA, Malkovskiy AV, Lazzareschi D, et al. 2015. Filamentous bacteriophage promote biofilm assembly and function. *Cell Host Microbe* 18:549–59
65. Mai-Prochnow A, Hui JGK, Kjelleberg S, Rakonjac J, McDougald D, Rice SA. 2015. Big things in small packages: the genetics of filamentous phage and effects on fitness of their host. *FEMS Microbiol. Rev.* 39:465–87
66. Hadas E, Marie D. 2006. Virus predation by sponges is a new nutrient-flow pathway in coral reef food webs. *Limnol. Oceangr.* 51:1458–550
67. Brown SP, LeChat L, DePaepe M, Taddei F. 2006. Ecology of microbial invasions: Amplification allows virus carriers to invade more rapidly when rare. *Curr. Biol.* 16:2048–52
68. Obeng N, Pratama AA, van Elsas JD. 2016. The significance of mutualistic phages for bacterial ecology and evolution. *Trends Microbiol.* 24:440–49
69. Nedialkova LP, Sidstedt M, Koeppel MB, Spriewald S, Ring D, et al. 2016. Temperate phages promote colicin-dependent fitness of *Salmonella enterica* serovar Typhimurium. *Environ. Microbiol.* 18:1591–603
70. Márquez LM, Roossinck MJ. 2012. Do persistent RNA viruses fit the trade-off hypothesis of virulence evolution? *Curr. Opin. Virol.* 2:556–60
71. Hartley MA, Bourreau E, Rossi M, Castiglioni P, Eren RO, et al. 2016. *Leishmaniavirus*-dependent metastatic leishmaniasis is prevented by blocking IL-17A. *PLOS Pathog.* 12:e1005852
72. Goodman RP, Freret TS, Kula T, Geller AM, Talkington MWT, et al. 2011. Clinical isolates of *Trichomonas vaginalis* concurrently infected by strains of up to four trichomonasvirus species (family *Totiviridae*). *J. Virol.* 85:4258–70
73. Goodman RP, Ghabrial SA, Fichorova RN, Nibert ML. 2011. *Trichomonasvirus*: a new genus of protozoan viruses in the family *Totiviridae*. *Arch. Virol.* 156:171–79
74. van Molken T, de Caluwe H, Hordijk CA, Leon-Reyes A, Snoeren TAL, et al. 2012. Virus infection decreases the attractiveness of white clover plants for a non-vectoring herbivore. *Oecologia* 170:433–44
75. Shapiro LR, Salvaudon L, Mauck KE, Pulido H, De Moraes CM, et al. 2013. Disease interactions in a shared host plant: effects of pre-existing viral infection on cucurbit plant defense responses and resistance to bacterial wilt disease. *PLOS ONE* 8:e77393
76. Xu P, Chen F, Mannas JP, Feldman T, Sumner LW, Roossinck MJ. 2008. Virus infection improves drought tolerance. *New Phytol.* 180:911–21
77. Davis TS, Pérez NAB, Foote NE, Magney T, Eigenbrode SD. 2015. Environmentally dependent host-pathogen and vector-pathogen interactions in the *Barley yellow dwarf virus* pathosystem. *J. Appl. Ecol.* 52:1392–401
78. Westwood JH, McCann L, Naish M, Dixon H, Murphy AM, et al. 2013. A viral RNA silencing suppressor interferes with abscisic acid-mediated signalling and induces drought tolerance in *Arabidopsis thaliana*. *Mol. Plant Pathol.* 14:158–70
79. 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* 315:513–15
80. Nakatsukasa-Akune M, Yamashita K, Shimoda Y, Uchiumi T, Abe M, et al. 2005. Suppression of root nodule formation by artificial expression of the *TrEnodDR1* (coat protein of *White clover cryptic virus 1*) gene in *Lotus japonicus*. *Mol. Plant-Microbe Interact.* 18:1069–80
81. Xu P, Liu Y, Graham RI, Wilson K, Wu K. 2014. Densovirus is a mutualistic symbiont of a global crop pest (*Helicoverpa armigera*) and protects against a baculovirus and Bt biopesticide. *PLOS Pathog.* 10:e1004490
82. Ryabov EV, Keane G, Naish N, Evered C, Winstanley D. 2009. Densovirus induces winged morphs in asexual clones of the rosy apple aphid, *Dysaphis plantaginea*. *PNAS* 106:8465–70

83. Abe H, Tomitaka Y, Shimoda T, Seo S, Sakurai T, et al. 2012. Anatagonistic plant defense system regulated by phytohormones assists interactions among vector insect, thrips and a tospovirus. *Plant Cell Physiol*. 53:204–12
84. Belliure B, Sabelis MW, Janssen A. 2010. Vector and virus induce plant responses that benefit a non-vector herbivore. *Basic Appl. Ecol.* 11:162–69
85. Bhattarai N, Stapleton JT. 2012. GB virus C: the good boy virus? *Trends Microbiol*. 20:124–30
86. Kernbauer E, Ding Y, Cadwell K. 2014. An enteric virus can replace the beneficial function of commensal bacteria. *Nature* 516:94–98
87. Barton ES, White DW, Cathelyn JS, Brett-McClellan KA, Engle M, et al. 2007. Herpesvirus latency confers symbiotic protection from bacterial infection. *Nature* 447:326–30
88. White DW, Keppel CR, Schnieder SE, Reese TA, Coler J, et al. 2010. Latent herpesvirus infection arms NK cells. *Blood* 115:4377–83
89. Furman D, Jojic V, Sharma S, Shen-Orr SS, Angel CJ, et al. 2015. Cytomegalovirus infection improves the immune responses to influenza. *Sci. Transl. Med.* 7:281ra43
90. Sandalova E, Laccabue D, Boni C, Tan AT, Fink K, et al. 2010. Contribution of herpesvirus specific CD8 T cells to antiviral T cell response in humans. *PLOS Pathog*. 6:e1001051
91. Patel MR, Emerman M, Malik HS. 2011. Paleovirology—ghosts and gifts of viruses past. *Curr. Opin. Virol.* 1:304–9
92. Katzourakis A. 2013. Paleovirology: inferring viral evolution from host genome sequence data. *Philos. Trans. R. Soc. B* 369:20120493
93. Strand MR, Burke GR. 2015. Polydnaviruses: from discovery to current insights. *Virology* 479–80:393–402
94. Whitfield JB. 2002. Estimating the age of the polydnavirus/braconid wasp symbiosis. *PNAS* 99:7508–13
95. Burke GR, Strand MR. 2012. Polydnaviruses of parasitic wasps: domestication of viruses to act as gene delivery vectors. *Insects* 3:91–119
96. Bézier A, Annaheim M, Herbinière J, Wetterwald C, Gyapay G, et al. 2009. Polydnaviruses of braconid wasps derive from an ancestral nudivirus. *Science* 323:926–30
97. Volkoff AN, Jouan V, Urbach S, Samain S, Bergoin M, et al. 2010. Analysis of virion structural components reveals vestiges of the ancestral ichnovirus genome. *PLOS Pathog*. 6:e1000923
98. Lander ES, Linton LM, Birren B, Nusbaum C, Zody MC, et al. 2001. Initial sequencing and analysis of the human genome. *Nature* 409:860–921
99. Stoye JP. 2012. Studies of endogenous retroviruses reveal a continuing evolutionary saga. *Nat. Rev. Microbiol.* 10:395
100. Johnson WE. 2015. Endogenous retroviruses in the genomics era. *Annu. Rev. Virol.* 2:135–59
101. Chuong EB, Elde NC, Feschotte C. 2016. Regulatory evolution of innate immunity through co-option of endogenous retroviruses. *Science* 351:1083–87
102. Esnault C, Cornelis G, Heidmann O, Heidmann T. 2013. Differential evolutionary fate of an ancestral primate endogenous retrovirus envelope gene, the EnvV *syncytin*, captured for a function in placentation. *PLOS Genet*. 9:e1003400
103. Lavialle C, Cornelis G, Dupressoir A, Esnault C, Heidmann O, et al. 2013. Paleovirology of '*syncitins*', retroviral *env* genes exapted for a role in placentation. *Philos. Trans. R. Soc. B* 368:20120507
104. Roberts RM, Green JA, Schulz LC. 2016. The evolution of the placenta. *Reproduction* 152:R179–89
105. Aswad A, Katzourakis A. 2012. Paleovirology and virally derived immunity. *Trends Ecol. Evol.* 27:627–36
106. Malfavon-Borja R, Feschotte C. 2015. Fighting fire with fire: endogenous retrovirus envelopes as restriction factors. *J. Virol.* 89:4047–50
107. Ryan F. 2009. *Virolution*. London: HarperCollins
108. Xu W, Eiden MV. 2015. Koala retroviruses: evolution and disease dynamics. *Annu. Rev. Virol.* 2:119–34
109. Faulkner GJ, Kimura Y, Daub CO, Wani S, Plessy C, et al. 2009. The regulated retrotransposon transcriptome of mammalian cells. *Nat. Genet.* 41:562–71
110. Maksakova IA, Mager DL, Reiss D. 2008. Keeping active endogenous retroviral-like elements in check: the epigenetic perspective. *Cell. Mol. Life Sci.* 65:3329–47
111. Meisler MH, Ting C. 1993. The remarkable evolutionary history of the human amylase genes. *Crit. Rev. Oral Biol. Med.* 4:503–9

112. Johnson R, Guigó R. 2014. The RIDL hypothesis: transposable elements as functional domains of long noncoding RNAs. *RNA* 20:959–76
113. Fatico A, Bozzoni I. 2014. Long non-coding RNAs: new players in cell differentiation and development. *Nat. Rev. Genet.* 15:7–21
114. Kassiotis G. 2014. Endogenous retroviruses and the development of cancer. *J. Immunol.* 192:1343–49
115. Gibb EA, Warren RL, Wilson GW, Brown SD, Robertson GA, et al. 2015. Activation of an endogenous retrovirus-associated long non-coding RNA in human adenocarcinoma. *Genome Med*. 7:22
116. Lamprecht B, Walter K, Kreher S, Kumar R, Hummel M, et al. 2010. Depression of an endogenous long terminal repeat activates the *CSF1R* proto-oncogene in human lymphoma. *Nat. Med.* 16:571–79
117. Trela M, Nelson PN, Rylance PB. 2016. The role of molecular mimicry and other factors in the association of human endogenous retroviruses and autoimmunity. *APMIS* 124:88–104
118. Chabannes M, Iskra-Caruana ML. 2013. Endogenous pararetroviruses—a reservoir of virus infection in plants. *Curr. Opin. Virol.* 3:615–20
119. Geering ADW, Maumus F, Copetti D, Choisne N, Zwicki DJ, et al. 2014. Endogenous florendoviruses are major components of plant genomes and hallmarks of virus evolution. *Nat. Commun.* 5:5269
120. Chen S, Kishima Y. 2016. Endogenous pararetroviruses in rice genomes as a fossil record useful for the emerging field of palaeovirology. *Mol. Plant Pathol.* 17:1317–20
121. Staginnus C, Gregor W, Mette MF, Teo CH, Borroto-Fernández EG, et al. 2007. Endogenous pararetroviral sequences in tomato (*Solanum lycopersicum*) and related species. *BMC Plant Biol*. 7:24
122. Noreen F, Akbergenov R, Hohn T, Richert-Pöggeler KR. 2007. Distinct expression of endogenous *Petunia vein clearing virus* and the DNA transposon *dTph1* in two *Petunia hybrida* lines is correlated with differences in histone modification and siRNA production. *Plant J.* 50:219–29
123. Kazazian HH Jr. 2004. Mobile elements: drivers of genome evolution. *Science* 303:1626–32
124. Kim A, Terzian C, Santamaria P, Pélisson A, Prud'homme N, Bucheton A. 1994. Retroviruses in invertebrates: The *gypsy* retrotransposon is apparently an infectious retrovirus of *Drosophila melanogaster*. *PNAS* 91:1285–89
125. Touret F, Guiguen F, Terzian C. 2014. *Wolbachia* influences the maternal transmission of the *gypsy* endogenous retrovirus in *Drosophila melanogaster*. *mBio* 5:e01529-14
126. Malik HS, Henikoff S. 2005. Positive selection of *Iris*, a retroviral *envelope*-derived host gene in *Drosophila melanogaster*. *PLOS Genet*. 1:e44
127. Nefedova LN, Kuzmin IV, Makhnovskii PA, Kim AI. 2014. Domesticated retroviral *GAG* gene in Drosophila: new functions for an old gene. *Virology* 450–51:196–204
128. Touret F, Guiguen F, Greenland T, Terzian C. 2014. In between: *gypsy* in *Drosophila melanogaster* reveals new insights into endogenous retrovirus evolution. *Viruses* 6:4914–26
129. Frank AC, Wolfe KH. 2009. Evolutionary capture of viral and plasmid DNA by yeast nuclear chromosomes. *Eukaryot. Cell* 8:1521–31
130. Aurélio Soares M, Amália de Carvalho Araújo R, Mendes Marini M, Márcia de Oliveira L, Gomes de Lima L, et al. 2015. Identification and characterization of expressed retrotransposons in the genome of the *Paracoccidioides* species complex. *BMC Genom*. 16:376
131. Esnault C, Levin HL. 2015. The long terminal repeat retrotransposons Tf1 and Tf2 of *Schizosaccharomyces pombe*. *Microbiol. Spectr.* 3. **https://doi.org/10.1128/microbiolspec.MDNA3-0040-2014**
132. Ashby MK, Warry A, Bejarano ER, Khashoggi A, Burrell M, Lichtenstein CP. 1997. Analysis of multiple copies of geminiviral DNA in the genome of four closely related *Nicotiana* species suggest a unique integration event. *Plant Mol. Biol.* 35:313–21
133. Crochu S, Cook S, Attoui H, Charrel RN, De Chesse R, et al. 2004. Sequences of flavivirus-related RNA viruses persist in DNA form integrated in the genome of *Aedes* spp. mosquitoes. *J. Gen. Virol.* 85:1971–80
134. Katzourakis A, Gifford RJ. 2010. Endogenous viral elements in animal genomes. *PLOS Genet*. 6:e1001191
135. Liu H, Fu Y, Jiang D, Li G, Xie J, et al. 2010. Widespread horizontal gene transfer from double-stranded RNA viruses to eukaryotic nuclear genomes. *J. Virol.* 84:11879–87
136. Chiba S, Kondo H, Tani A, Saisho D, Sakamoto W, et al. 2011. Widespread endogenization of genome sequences of non-retroviral RNA viruses into plant genomes. *PLOS Pathog*. 7:e1002146

137. Belyi VA, Levine AJ, Skalka AM. 2010. Sequences from ancestral single-stranded DNA viruses in vertebrate genomes: The *Parvoviridae* and *Circoviridae* are more than 40 to 50 million years old. *J. Virol.* 84:12458–62
138. Belyi VA, Levine AJ, Skalka AM. 2010. Unexpected inheritance: multiple integrations of ancient bornavirus and ebolavirus/marburgvirus sequences in vertebrate genomes. *PLOS Pathog.* 6:e1001030
139. Horie M, Kobayashi Y, Suzuki Y, Tomonaga K. 2013. Comprehensive analysis of endogenous bornavirus-like elements in eukaryote genomes. *Philos. Trans. R. Soc. B* 368:20120499
140. Fujino K, Horie M, Honda T, Merriman DK, Tomonaga K. 2014. Inhibition of Borna disease virus replication by an endogenous bornavirus-like element in the ground squirrel genome. *PNAS* 111:13175–80
141. Chu H, Jo Y, Cho WK. 2014. Evolution of endogenous non-retroviral genes integrated into plant genomes. *Curr. Plant Biol.* 1:55–59
142. Roossinck MJ. 2012. Persistent plant viruses: molecular hitchhikers or epigenetic elements? In *Viruses: Essential Agents of Life*, ed. G Witzany, pp. 177–86. Dordrecht, Neth.: Springer
143. Thézé J, Leclercq S, Moumen B, Cordaux R, Gilbert C. 2014. Remarkable diversity of endogenous viruses in a crustacean genome. *Genome Biol. Evol.* 6:2129–40
144. Taylor DJ, Bruenn J. 2009. The evolution of novel fungus genes from non-retroviral RNA viruses. *BMC Biol.* 7:88
145. Bell-Sakyi L, Attoui H. 2013. Endogenous tick viruses and modulation of tick-borne pathogen growth. *Front. Cell. Infect. Microbiol.* 3:25
146. Feng G, Leem YE, Levin HL. 2012. Transposon integration enhances expression of stress response genes. *Nucleic Acids Res.* 41:775–89