The good viruses: viral mutualistic symbioses

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Abstract | Although viruses are most often studied as pathogens, many are beneficial to their hosts, providing essential functions in some cases and conditionally beneficial functions in others. Beneficial viruses have been discovered in many different hosts, including bacteria, insects, plants, fungi and animals. How these beneficial interactions evolve is still a mystery in many cases but, as discussed in this Review, the mechanisms of these interactions are beginning to be understood in more detail.

Mutualistic
Pertaining to a symbiosis that is beneficial to all partners.

Provirus
Viral genomic DNA that has integrated into the genome of the host cell.

Symbiogenic
Pertaining to a new species: formed by the fusion of symbiotic organisms.

Antagonism
A symbiotic relationship in which one partner benefits at the expense of the other.

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Viruses have long had a 'bad rap'; since the discovery of tobacco mosaic virus (TMV) in the 1890s[1], they have been largely viewed as pathogens. This bias has led to a misunderstanding about viruses, and few researchers have looked specifically for viruses that might be beneficial to their hosts[2]. Although it cannot be denied that viruses have caused extensive disease and suffering for humans and domesticated plants and animals, there are many viruses that are clearly mutualistic (TABLE 1). Some are essential for the survival of their hosts, others give their hosts a fighting edge in the competitive world of nature and some have been associated with their hosts for so long that the line between host and virus has become blurred. In this Review, I look at several examples of viruses that are beneficial to their hosts and examine how these beneficial functions work. In some cases, we have a detailed understanding of the mechanisms of these mutualistic interactions, and in other cases we can speculate on the mechanisms involved.

The problem of definitions

Several concepts outlined in this Review do not have universally accepted definitions. It is therefore worthwhile to begin by clarifying the most important terms in some detail.

What is a virus? Defining a virus is a challenge, even for those who have spent their lives working on viruses. In 1997, a group of virologists held a workshop in Santa Rosa National Park, Liberia, Costa Rica, to discuss the logistics of creating an inventory of virus biodiversity. It quickly became clear that there was no accepted definition of a virus, so as part of the workshop, viruses were defined as follows: "intracellular parasites with nucleic acid capable of directing their own replication, that do not serve any essential function for their host, have an extrachromosomal phase and are not cells". This seemed like a good definition at the time, and could be construed to include viroids and plasmids, but it does not include the endogenized retroviruses that are now known to be abundant in most eukaryotic genomes, or the integrated proviruses of bacteria (about which there has been a long historical discussion[3]), and it also does not do justice to the numerous examples of beneficial viruses, which are the focus of this Review.

The beneficial effects of viruses range from obligate mutualisms, in which the survival of the host is dependent on the virus, to benefits that occur only under specific environmental conditions. In addition, some of these relationships are ancient and the line between the virus and its host is blurry, and some relationships are clearly symbiogenic, such as the relationship between braconid wasps and polydnaviruses (discussed below). Hence, a clear definition of a virus might not be possible, but for the purposes of this article, the Costa Rica definition can be modified as follows: 'intracellular parasites with nucleic acids that are capable of directing their own replication and are not cells'.

What is symbiosis? The term 'symbiosis' was first coined in the nineteenth century to describe lichen, an entity composed of a fungus and an alga living intimately together[4]. Beatrix Potter, who studied fungi and lichen early in her life (but is better known for writing children's stories than for her work in mycology), first proposed that both the fungus and the alga benefit from the symbiosis, so the relationship is mutualistic. In this article, I use the original definition for symbiosis: 'two dissimilar entities living in an intimate association'. Although often confused with mutualism, symbiosis actually encompasses several different relationships, including antagonism,

Table 1 | **Types of virus–host mutualism**

Virus group	Hosts	Beneficial effect	Type of mutualism
Polydnaviruses	Parasitoid wasps	Required for survival of the wasp egg in its insect host	Symbiogenic
Retroviruses	Mammals	Involved in the evolution of the placenta	Symbiogenic
Pararetroviruses	Plants	Protect against pathogenic viruses	Symbiogenic
Herpesviruses	Humans	Suppress HIV infection	Conditional mutualism
	Mice	Protect against bacterial infection	Conditional mutualism
Parvoviruses	Aphids	Required for the development of wings	Conditional mutualism
Phages	Bacteria	Allow the invasion of new territory by killing off competitors	Conditional mutualism
		Allow the invasion of mammalian hosts	Mutualism
Yeast viruses	Fungi	Allow the suppression of competitors	Conditional mutualism
Fungal viruses	Fungi and plants	Confer thermal tolerance to fungal endophytes and their plant hosts	Mutualism
Plant viruses	Plants	Confer drought and cold tolerance	Conditional mutualism

commensalism and mutualism. In fact, in most cases the symbiotic relationship cannot be strictly classified as belonging to only one of these three categories and can vary with the environment or other circumstances.

There can be several interpretations of 'intimate', but most people would agree that all viruses have an intimate relationship with their hosts. Symbiosis can be obligate, meaning that the relationship is required for the survival of one or both partners, or non-obligate. Viruses are obligate symbionts in that they cannot replicate outside their hosts. Although they are often thought of as purely antagonistic, examples of mutualistic viruses have been described for several decades.

What is mutualistic symbiosis? Mutualisms are relationships between living entities in which each member benefits from the relationship, although it should be pointed out that mutualisms can also exist between partners that are not in a symbiotic relationship. According to most ecology textbooks, mutualism must result in increased fitness, as measured by increased reproduction. However, I use the term 'mutualistic symbiosis' more loosely here, to describe any symbiotic relationship in which all partners benefit. Mutualistic symbioses can be conditional, so that in some circumstances there is a benefit and in other circumstances there is a cost.

In this Review, I describe viruses that have mutualistic symbiotic relationships with their hosts. These include viruses that have a long association with the host, so that the relationship has become essential for the survival of the host; viruses that attenuate diseases caused by other viruses or other pathogens; viruses that are useful to their hosts because they kill competitors; viruses that help their hosts adapt to extreme environmental changes; and viruses that are involved in complex multispecies interactions.

Symbiogenic viruses

Some ancient relationships between viruses and their hosts have resulted in the viruses becoming part of their hosts in a process known as symbiogenesis. This refers to a fusion of two symbiotic entities, leading to a new species, and is probably a common means by which viruses themselves speciate[5]. Some virologists think that modern genomes are essentially remnants of ancient viruses[6,7]. Although some of these relationships are probably so ancient they can no longer be detected reliably, other relationships are quite clear. The increase in the availability of genome sequence information for many organisms will undoubtedly reveal many more examples.

Viruses of endoparasitoid wasps. The polydnaviruses ('poly-DNA'; that is, referring to the genomes of these viruses, which comprise many DNA segments) are the best studied mutualistic viruses. There are thousands of these viruses; an estimated 30,000 species of endoparasitoid braconid and ichneumonid wasps probably have their own mutualistic viral species (called bracoviruses and ichnoviruses, respectively)[8,9]. The relationships between these viruses and their wasp hosts are ancient, and some researchers have questioned whether these viruses are really viruses anymore[10]. The genes involved in viral replication and packaging have moved to become part of the wasp genome, and the virions package wasp genes that are expressed after the wasp has deposited its eggs into its lepidopteran insect host[8,11] (FIG. 1).

Many parasitoid wasps lay their eggs in a living insect larva. The innate immune system of the larva would normally wall off the egg, forming an encapsulation structure that prevents the egg from developing, but the wasp genes carried by the polydnavirus virions suppress this response. Without this suppression, the wasp eggs would not survive[12].

Parasitoid wasps are often vectors for viruses that are pathogens of the wasps' insect hosts. Both ascoviruses (insect DNA viruses that are distantly related to polydnaviruses) and reoviruses (RNA viruses that include genera which infect plants, fungi, insects, fish and mammals) have wasp vectors, and some of these viruses are also mutualists of these vectors. Diadromus pulchellus ascovirus 4 (DpAV4), from the wasp *Diadromus pulchellus*,

Commensalism
A symbiotic relationship in which one partner benefits and the other is unaffected.

Endoparasitoid
A specific type of parasitoid organism that spends a portion of its life within another organism.

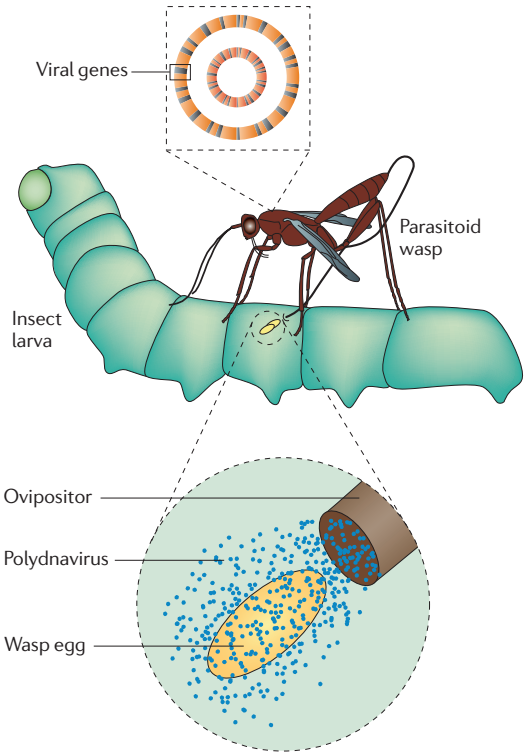

Figure 1 | **The relationship between polydnaviruses, wasps and caterpillars.** Many parasitoid wasps lay their eggs inside a living insect larva. When a female wasp deposits her eggs inside a lepitdopteran caterpillar, she also deposits her symbiogenic polydnavirus virions, which only express wasp genes. These genes are expressed in the caterpillar, where they prevent the encapsulation process that would otherwise wall off and kill the wasp egg.

inhibits the deposition of melanin, an important component of the wasp egg encapsulation structure. When DpAV4 is injected experimentally into an insect host, it replicates rapidly and the insect dies before the parasitoid can develop. However, in the wasp, DpAV4 is found in conjunction with a reovirus, Diadromus pulchellus idnoreovirus 1 (DpRV1), which may delay the replication of DpAV4 to allow the insect to survive long enough for the wasp eggs to develop. This is thought to be mediated by an additional RNA that is packaged in the DpRV1 virions and is not part of the viral genome but is derived from the female wasp (DpRV1 virions isolated from female wasps have an additional RNA that is not present in virions isolated from male wasps)[13,14]. To the reductionist-minded experimentalist, this system seems extremely complicated, but in nature such interactions are probably very common. However, this complexity is one reason why few of the mechanisms of mutualistic symbioses involving viruses have been well characterized.

Another reovirus, DpRV2, is the only reovirus from *D. pulchellus* that has been found to exist without co-infection of other viruses. DpRV2 also inhibits melanization of the wasp egg encapsulation structure and is therefore a mutualist of the wasp[14]. In another wasp–virus mutualism, Diachasmimorpha longicaudata entomopoxvirus (DlEPV), from the braconid wasp *Diachasmimorpha longicaudata*, replicates in both the wasp and in the fruitfly that the wasp parasitizes, and it suppresses the immune response of the fruitfly[15]; hence, this virus is an antagonist of the fruitfly and a mutualist of the wasp.

It is not clear why there are so many examples of mutualistic viruses in the parasitoid wasps, but it is possible that the antagonistic symbiotic relationship between the wasps and their insect hosts allowed the wasp larvae to acquire insect pathogens that subsequently evolved to benefit the wasp[16]. Recently, it was proposed that the proteins of ichnoviruses contain motifs derived from ascoviruses[17]; however, another recent paper shows that the structural proteins of the ichnoviruses are not related to those of ascoviruses but are derived from a different, unidentified virus group[18]. What is clear from this and other studies is that the bracoviruses have a different origin from that of the ichnoviruses, in another insect virus group, probably the nudiviruses[11].

Endogenous retroviruses. Intact and fragmented retroviruses are found in the genomes of almost all eukaryotes. Approximately 8% of the human genome is derived from retroviruses[19], and this percentage increases dramatically if other mobile elements are included[20]. Many of these retroviruses are conserved in humans and other primates, indicating that the endogenization events occurred a long time ago. In fact, all of the endogenous retroviruses in humans are at least thousands of years old[21]. For a retrovirus to become endogenized, it must infect germline cells. There is a large body of literature regarding endogenized retroviruses (see, for example, REFS 22–29) and their role in genome evolution[30]; here, I consider a few notable examples of endogenous retroviruses that seem to have a beneficial effect on their hosts.

Why are endogenous retroviruses there? One hypothesis is that each one represents a plague-culling event: endogenization may result in immunity to an otherwise lethal virus, so only individuals with the endogenized retrovirus survive[31]. There is some evidence for this hypothesis, in the form of the ongoing endogenization of a retrovirus in Australian koalas[32]. Koalas from northern mainland Australia harbour the endogenized version of the koala retrovirus (KoRV). Koala populations from Kangaroo Island, which lies off the south coast of Australia, lack KoRV completely, and those in the southern mainland are not uniformly infected, probably because the dwindling koala populations here have been bolstered by the introduction of individuals from Kangaroo Island[31]. The endogenized KoRV has undergone genetic changes that have attenuated the virus compared with closely related virulent exogenous retroviruses from other mammals[33]. In addition, many animals harbouring the endogenized KoRV do not suffer from any KoRV-associated disease (such as lymphomas and leukaemias) and might be immune to acute infections with exogenous KoRV[31]. The mainland and Kangaroo Island populations have been separated for at least 100 years, so this process has been occurring over

Box 1 | **A beneficial virus and horizontal gene transfer?**

The larva of the sea slug *Elysia chlorotica* attaches to a specific algal species, and if it does not find this alga, it does not mature further[104]. After attaching to the alga, the young slug feeds on it and acquires its chloroplasts. Remarkably, the chloroplasts remain functional in the adult slugs for about 9 months and provide energy to the slug. Chloroplasts do not encode all the genes that they need in order to function, as many of the necessary gene products are encoded in the plant nucleus, so chloroplasts are usually not functional after ingestion. In *E. chlorotica*, however, the algal genes required for chloroplast function are found in the nucleus of the slug at all of the key life cycle stages (egg, larva and adult)[105]. The *E. chlorotica* genome also contains an endogenous retrovirus[106].

At 9 months old, the adult slugs lay eggs and, in a highly synchronous manner, the whole adult population dies. At this synchronous end of life, all of the adult slugs have a high titre of an exogenous version of the endogenous retrovirus[104]. The role of the virus in this complex relationship has not been clearly defined, but it has been proposed that it is involved in the synchronous die off, and that the virus is the vehicle for the horizontal gene transfer, from the algal nucleus to the slug, of genes for chloroplast functions[104–106].

the past century[32,34]. This provides a unique opportunity for understanding the endogenization process and its effect on the host.

At least some endogenous retroviruses encode functional genes and are thought to be involved in major evolutionary leaps. For example, the evolution of placental mammals probably occurred after the endogenization of a retrovirus[35]. Retroviral envelope proteins (Env proteins) cause fusion of cell membranes, a process that not only allows invasion of oncogenic viruses but also is required for the development of the placental syncytium, an essential part of the barrier that prevents maternal antigens and antibodies getting into the fetal bloodstream. In sheep, the endogenous Jaagsiekte sheep retrovirus (JRSV) *env* is expressed at high levels in the genital tract of ewes, and when the virus is suppressed by antisense expression, pregnant sheep abort[36].

Sometimes, there is a fine line between antagonism and mutualism. The exogenous form of JSRV can infect the respiratory tract of sheep and cause pulmonary cancer. It has been speculated that the exogenous virus was prevented from infecting sheep by the genital route because of the endogenization process, but it later evolved to infect sheep by an alternative route[37].

Endogenous pararetroviruses of plants. Plants harbour numerous endogenous pararetroviruses (pararetroviruses package DNA rather than RNA), and in some cases these viruses can still excise from the genome and become infectious to other plants. This often occurs after crossing of different plant species (see REF. 38 for a review). A tomato endogenous pararetrovirus sequence (*Lyc*EPRV) generates small interfering RNAs (siRNAs)[39] that are important in plant defence against viruses and are thought to protect the tomato against infection by exogenous *Lyc*EPRV and other related viruses. The expression of two classes of siRNAs, the 21-mers and 22-mers, is increased during infection by other plant viruses that contain silencing suppressors, such as potato virus Y (for reviews on RNA-based silencing of plant viruses, see REFS. 40,41). The endogenous sequences of the *Lyc*EPRVs are highly methylated, but they are still expressed and have been found in tomato expressed sequence tag (EST) libraries. *Lyc*EPRV does not seem to exogenize (that is, excise from the genome to become an infectious virus), even after crosses with related species[39].

In petunia, the situation is different. An endogenous virus, petunia vein-clearing virus, is silenced by methylation and chromatin effects, and very little to no siRNA is detected unless the endogenous virus is exogenized. It seems that in this case, siRNA does not contribute to immunity but may play a part in preventing infectious viruses from entering the petunia meristem[42].

In banana (the genus *Musa*), the endogenized pararetrovirus banana streak virus (BSV) can exogenize and establish acute infections. The endogenous forms of BSV are highly diverged in different species of *Musa*, indicating that endogenization probably occurred several times in this plant genus[38]. To date, no positive effect of the endogenous virus has been found in bananas[43].

Other roles for retroviruses include horizontal gene transfer, which probably occurs during exogenization and subsequent endogenization in a new host. In some cases, this process could clearly be beneficial, such as when the host acquires new genetic material (BOX 1).

Beneficial viruses in mammalian diseases

Although the literature about the involvement of viruses in mammalian diseases is replete with examples of pathogenic viruses, there are also a few examples of viruses that are beneficial to mammals.

An early example was the study of adenovirus in hamsters. Human adenovirus type 12 causes cancerous tumours in newborn hamsters at rates of over 50%, depending on the titre of the inoculum[44]. However, when the newborn hamsters also receive adeno-associated virus, the number of tumours is dramatically decreased[44]. In patients infected with HIV-1, some long-term studies have found that patients progress to full-blown AIDS much more slowly if they are also infected with hepatitis G virus, a non-pathogenic hepatitis virus that is common in humans[45,46]. Infection with human cytomegalovirus has also been reported to suppress superinfection with HIV-1 (REF. 47), and hepatitis A virus can suppress infection with hepatitis C virus[2,48]. The protecting viruses interfere with various functions of the more pathogenic viruses, including replication.

Viruses can also protect against non-viral diseases. For example, type 1 diabetes could be prevented in a mouse model by infection with lymphotropic viruses[49]. Several oncolytic viruses that can attack human cancers have been discovered or engineered (reviewed in REFS. 50–53). Mice that are latently infected with either murine gammaherpesvirus 68 (which is related to the human pathogen Epstein–Barr virus) or murine cytomegalovirus (which is related to human cytomegalovirus) are protected from infection by both *Listeria monocytogenes*, the causative agent of a serious foodborne illness in humans, and *Yersinia pestis*, the causative agent of plague. The viruses modulate the host immune system by stimulating innate immunity[54].

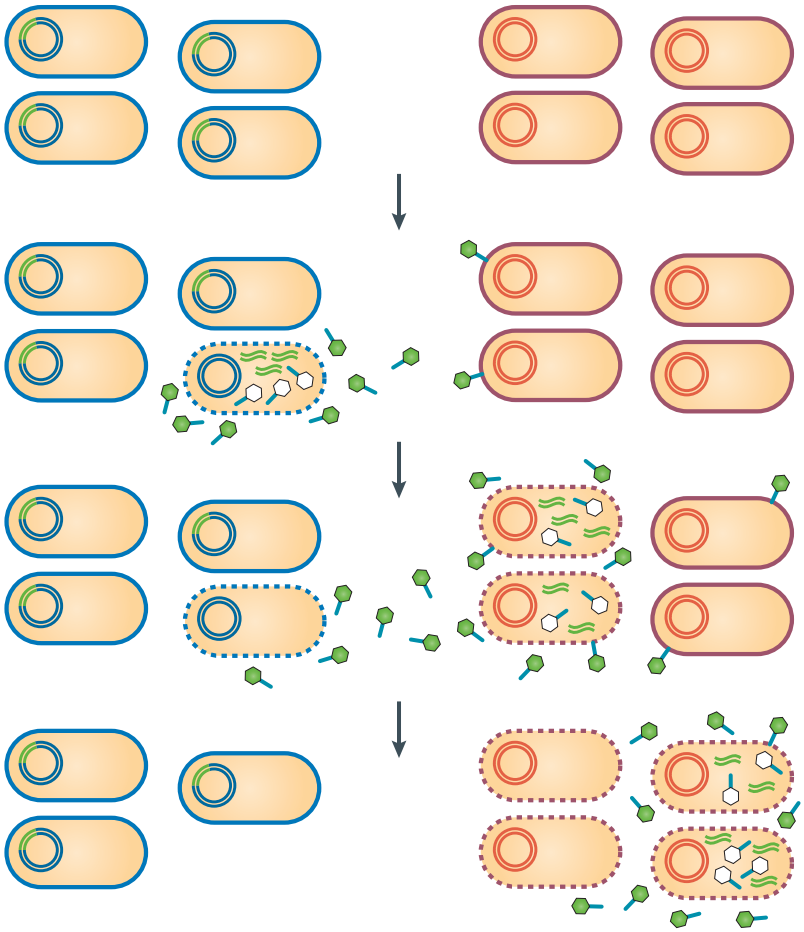

Figure 2 | **Viruses as natural weapons.** Many bacteria carry a viral genome (green) integrated into their own genome (blue). These lysogenic viruses remain dormant and render the host bacteria immune to lytic forms of the virus. If the lysogenic virus excises from the genome, it can reproduce rapidly, producing thousands of progeny and leading to the death of the host cell. This releases the viruses into the extracellular environment, where they can kill competing bacteria (red) that are not lysogenic for the virus.

In general, this area of research has received little attention, but these examples show that human medicine may benefit from taking mutualistic viruses more seriously[2].

Viruses as natural weapons

Bacteria and yeasts have evolved systems to beat their competitors by killing them with the aid of viruses. This strategy almost certainly also occurs when other organisms, including humans, invade new territory, and it could account for some of the success of invasive species.

Killer phages. Bacterial viruses — or phages — can exist for many generations integrated into the genomes of their hosts, a condition that is known as lysogeny. Bacteria harbouring lysogenic phages are immune to the infectious — or lytic — forms of the virus[55]. In some bacterial populations, a few bacterial cells will convert the lysogenic phages to a lytic cycle. In this cycle, the lysogenic phage excises from the genome and reproduces rapidly, producing thousands of progeny and killing the host cell in the process. The death of the host cell releases the viruses into the extracellular environment, where they can kill competing bacteria that are not lysogenic for the virus[56]. The lytic cell is sacrificed for the benefit of the remaining lysogenic population of bacteria, allowing the invasion of new territory (FIG. 2).

In an alternative strategy, some bacteria harbour phages that produce a toxin to which the bacterial host is insensitive. The release of the toxin destroys bacteria that do not host the phage. This strategy seems to provide a better system for competing with other bacteria present in the environment inhabited by a population, whereas the use of lytic phages allows bacteria to invade new territory[57].

Killer yeasts. Killer yeasts do not release their viruses to kill off their competitors; rather, the viruses that yeasts host in a persistent manner can produce toxins that kill competitors, whereas the host yeast remains immune[58]. Killer yeasts were first found in the brewing industry, when a contaminant yeast killed off normal brewing strains[59]. The viruses are transmitted vertically in the yeast, as well as through sexual conjugation and anastamosis (a process in which closely related fungal cells form cytoplasmic junctions). As the viruses do not seem to have a true extracellular phase, they are not thought to be transmitted horizontally, but this has not been rigorously explored[58,60]. As is true in many symbioses, the nature of the relationship between virus and host is dependent on the environment: at high pH, the toxin is much less effective and the benefit is lost. In addition, a change in host ploidy can convert the mutualist into a liability. Thus, during the asexual diploid stage of the host's life cycle, the virus allows invasion of new territory by killing off competitors, but in the sexual haploid stage, the virus does not kill off competitors. This is an advantage for the virus, because its major means of spread is through sexual mating[61].

Animal and plant invaders. Wild animals often harbour large numbers of persistent viruses, which can be the same viruses that can cause serious pathology in other, related animals. The persistent infection seems to protect the animals from the acute phase of infection with the exogenous virus, but it can provide a source of acute virus that can wipe out a population of related, sensitive animals. This scenario can allow invasion of new territory or can protect a resistant population from invasion by a sensitive population[62]. In plants, invasive species can bring viruses with them that contribute to the process of invasion by weakening competing native species, as exemplified by the invasive annual grasses that are outcompeting native bunchgrass in California, USA[63]. The process of invasion has not been well studied, and there may be many more examples that involve viruses.

Human invasions. Human history is filled with examples of invasions of new territory. Recent estimates indicate that 90% of the native human population in the Americas died within 10 years of the European invasions.

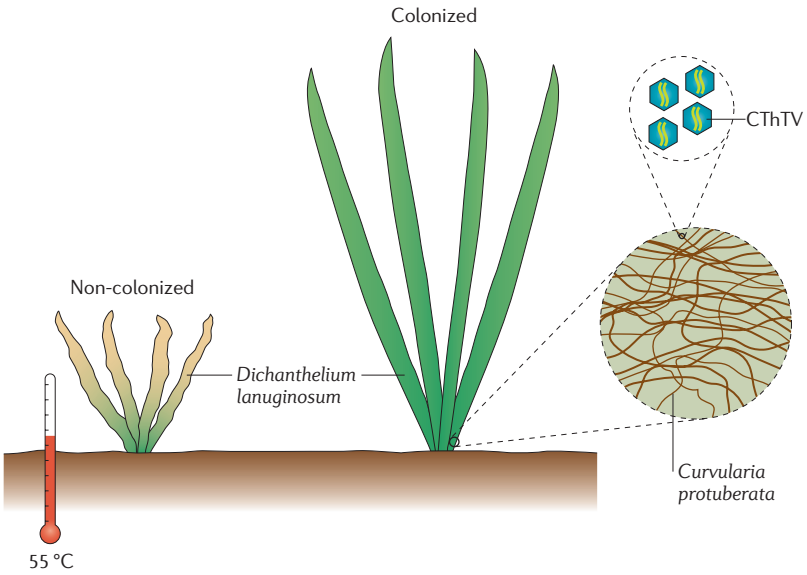

Figure 3 | **A three-way mutualistic symbiosis.** The panic grass *Dichanthelium lanuginosum* is found in geothermal soils in Yellowstone National Park, USA, where it can grow at soil temperatures >50 °C. The plant requires a fungal endophyte, *Curvularia protuberata*, to survive at this temperature. In turn, the fungus requires a virus, Curvularia thermal tolerance virus (CThTV), to confer this thermotolerance effect.

Although wars and massacres accounted for some of this, many native peoples were exterminated by viral infections, including smallpox, influenza and even the common cold (caused by rhinoviruses)[64,65]. The native populations had never been exposed to these viruses and had no immunity. A similar scenario with smallpox is thought to have decimated the Australian Aboriginal populations in the nineteenth century[66]. In all of these examples, viruses carried by the invading populations benefited the invaders by clearing the new territory of its native inhabitants. However, the long-term effects on the human gene pool might have been less beneficial for the species as a whole.

Fungal viruses

Viruses are common in fungi. Fungal viruses are persistent, and clear examples of horizontal transmission are rare, although transmission is known to occur through anastomosis. Anastomosis occurs only between fungi of the same species, and usually the same strain, so this method of transmission does not introduce viruses to new species. Phylogenetic analyses suggest that there are other modes by which viruses can be transmitted between fungal species[67], but this has not been demonstrated in any laboratory experiments.

In most cases, the role of viruses in the life of fungi is not known. However, in some plant-pathogenic fungi, the virus can act as a mutualist of the plant by attenuating the pathology of the fungus[68]. The best studied example of this is chestnut blight, which is caused by the fungus *Cryphonectria parasitica*. When the fungus harbours Cryphonectria hypovirus, the pathology of the fungus on the plant is greatly reduced[68]. This system has been proposed as a method to rejuvenate the chestnut forests that once covered most of the eastern United States, but the lack of transmission makes the practical applications complicated[69,70]. A few other examples of hypovirulence-associated viruses in plant-pathogenic fungi have been found, including in *Ophiostoma ulmi* (the causative agent of Dutch elm disease[71]), *Cochliobolus victoriae* (the causative agent of Victoria blight of oats[72]) and *Sclerotinia sclerotiorum* (the causative agent of white mould[73]). These viruses, although not mutualists of their fungal hosts, are beneficial for the plants that harbour their fungal hosts.

In one case, a fungal virus is an obligate partner in a complex three-way mutualistic symbiosis that allows plants to grow in geothermal soils in Yellowstone National Park, USA. A panic grass, *Dichanthelium lanuginosum*, which grows in soils with temperatures of >50 °C, requires a fungal endophyte, *Curvularia protuberata*, to survive. This is a clear mutualism, because the fungus cannot grow at high temperatures in culture[74]. Subsequently, a virus was discovered in the fungus, and it was shown that fungal strains cured of the virus did not confer thermotolerance to the plants. If the virus, Curvularia thermal-tolerance virus, was reintroduced to the virus-free fungus through anastomosis, the thermotolerance was restored[75] (FIG. 3). The mechanism of this thermotolerance seems to be complex and may involve control of plant and/or fungal gene products that are involved in stress tolerance. A comparison of the transcriptomes of fungi with and without the virus under mild heat stress[76] implicated genes involved in the synthesis of trehalose, a sugar that is known to confer drought and heat tolerance in other fungi[77], and melanin, a pigment that is associated with abiotic-stress tolerance in fungi[78].

How this relationship was established is not yet clear, but it is known that the environment of these plants changes rapidly, as the geothermal features in Yellowstone National Park are constantly changing. Without its symbionts, *D. lanuginosum* could not survive. It seems logical that a virus would provide the genetic information needed to allow this rapid adaptation, because viruses have extreme levels of diversity and can evolve rapidly to encode new functions.

Plant viruses

Plant viruses are mostly known to cause diseases in crops, but several disease-causing plant viruses display conditional mutualism and confer drought or cold tolerance to their hosts. When *Nicotiana benthamiana* plants (a relative of tobacco) are infected with TMV, cucumber mosaic virus (CMV), brome mosaic virus (BMV) or tobacco rattle virus (TRV), they survive longer after water is withdrawn than uninfected plants[79]. The same is true for rice infected with BMV, for tobacco infected with TMV, and for beet, cucumber, pepper, watermelon, squash, tomato, *Chenopodium amaranticolor* and *Solanum habrochaites* (wild relative of tomato) infected with CMV[79]. In addition, beets infected with CMV survived cold treatments that killed uninfected plants[79]. The mechanism for this remarkable observation is not known, but a profile of the metabolites in the BMV-infected rice and the CMV-infected beets

Box 2 | **Tulip breaking virus**

Tulips were first domesticated in Turkey and Iran, and they became popular, albeit difficult to obtain, in the Netherlands in the late sixteenth century. The Dutch were referred to as tulipomaniacs because of their obsession with these flowers; they particularly liked striped tulips, which became the most sought-after and coveted tulips in Europe and were the subject of many still-life paintings (see the figure; the tulip on the left is striped compared with that on the right)[107]. The published price for a single bulb of the striped tulip known as Semper Agustus was 3,000 guilders in the 1630s, which was enough to buy an entire ship and all its contents. However, the striping, or colour breaking, in the flowers was not very stable and was often lost in progeny bulbs. Furthermore, no one could tell by looking at a bulb whether the flowers would maintain their stripes. Investing in tulips became a form of gambling, and it is now considered to be the first known economic bubble[84,107].

In the twentieth century, striped tulips were found to be harbouring a virus — tulip breaking virus — and plants cured of the virus lost their stripes. The mechanism for the colour breaking involves the virus interfering with the synthesis of pigments in the flowers[84]. There are numerous other colour-breaking viruses in flowering plants, although colour breaking in modern tulips is now usually genetic, as growers prefer to keep their tulips looking the same bulb after bulb.

Image courtesy of K. Horst and K. Loeffler, Cornell University, Ithaca, New York, USA.

showed that the levels of several plant osmoprotectants were higher in virus-infected plants than in uninfected plants[79]. There are no other reports of this phenomenon in the literature, although a study on the productivity of sugar beets reported yield losses in plants carrying a persistent virus (beet cryptic virus), except under drought conditions, when yields in the virus-infected plants were the same as those in the uninfected plants[80].

Many plants harbour persistent viruses[81] that have been poorly studied. In surveys of wild plants[82], persistent viruses make up around half of the viruses found (M.J.R., unpublished observations). However, at least one persistent virus, white clover cryptic virus, encodes a gene that the host uses under certain conditions. This gene is in fact the viral coat protein, but it was discovered in an EST library of white clover during nodulation and seems to suppress nodulation when sufficient nitrogen is present[83]. As vertically transmitted persistent viruses remain with their plant hosts for many generations, and perhaps for thousands of years, it seems likely that plants have evolved novel uses for viral genes. More detailed genomic analyses are likely to reveal more of these relationships.

Some plant viruses have a dramatic effect on the appearance of plants, a famous example being tulip breaking virus[84] (see BOX 2). Tulip breaking virus is not a true mutualist because the plants do not benefit from its presence, although perhaps one could argue that the beauty of the symptoms resulted in humans coveting and propagating the virus-infected plants over all other forms of tulip.

Insects and the viruses they transmit

Geminiviruses and insects. *Bemisia tabaci* biotype B is an invasive whitefly species that has emerged worldwide in recent decades[85]. It is a vector for several plant DNA viruses called geminiviruses that can result in huge crop losses[86]. In China, *B. tabaci* biotype B has largely displaced the native biotype, *B. tabaci* ZHJ1[87]. After the arrival of *B. tabaci* biotype B, two geminiviruses emerged — tobacco curly shoot virus (TbCSV)[88] and tomato yellow leaf curl China virus (TYLCCNV)[89] — that are transmitted by this whitefly. *B. tabaci* biotype B insects fed on tobacco plants infected with either virus had increased fecundity and longevity compared with those fed on uninfected tobacco, with the benefits being greater in TYLCCNV infection than in TbCSV infection. No changes were seen in the native *B. tabaci* biotype ZHJ1 (REF. 90). Hence, TbCSV and TYLCCNV seem to be mutualists of *B. tabaci* biotype B. However, these viruses are persistently transmitted, meaning that after the insect acquires one of these viruses, it is carried for an extended period. For *B. tabaci* biotype B, TbCSV-carrying insects have a similar lifespan but greater fecundity, whereas TYLCCNV-carrying insects have a shorter lifespan and lower fecundity, compared with uninfected insects. For the native whitefly, there was no change in either fecundity or longevity with TbCSV infection, but both were reduced with TYLCCNV infection[90]. Again, the relationships are complicated. Both viruses make the plant a better host for the invasive insects; transmission of one virus, TbCSV, benefits the invasive insect, and transmission of the other virus, TYLCCNV, is antagonistic to both insects. In other related studies, similar benefits and costs have been seen[91].

Mosquitoes and viruses. One of the earliest examples of viruses with a mutualistic role in their symbiotic partners is provided by viruses that have mosquito vectors. During feeding, mosquitoes must find their blood meal as rapidly as possible to prevent being killed by an annoyed host. *Aedes aegypti*, a mosquito vector of many parasites, was able to locate a host blood vessel more rapidly after feeding on hamsters infected with Rift Valley fever virus than after feeding on uninfected hamsters. The authors of this study speculated that the potential of the virus to disrupt haemostasis (that is, its ability to stop blood flow) could be the cause of this enhanced ability to find a blood vessel[92]. Hence, Rift Valley fever virus seems to have a beneficial role in the life of the mosquito and thus enhances its own acquisition and transmission by the insect.

Conditional mutualists in* Drosophila *spp. *Drosophila* spp. can be infected by several viruses; most are commensals, but a few are pathogens[93]. However, Drosophila C virus (DCV) can be either a pathogen or a mutualist, depending on the age of the infected fly. In young flies, DCV is a pathogen and reduces the survival of prepubescent flies during natural infections, which occur by ingestion of infected food. However, infected adult flies get a boost in their reproductive

capacity, and the overall effect of the virus on fly populations is positive[94]. DCV has been used in recent years to study defence responses in *Drosophila* spp., but most of these studies have involved injecting viruses into *Drosophila* spp., and under these circumstances the viruses are always pathogenic[94] . The route of infection is clearly important; for example, ingested viruses would not encounter the same immune response as injected viruses. This illustrates one of the difficulties in studying the interactions of mutualistic viruses: experimental infections often have different outcomes from natural infections. The evolution of host–virus interactions has occurred outside of the laboratory, but by studying these interactions in a modified and controlled laboratory environment, we often change their outcomes, contributing to the overall bias of the perception of viruses as pathogens.

Conditional mutualism of aphid viruses. Asexually reproducing aphids generally have two forms, or morphs: winged and wingless. The wingless morphs have higher fecundity, which allows rapid colony expansion when conditions are good (for example, when the weather is warm and plants for feeding are plentiful). However, the winged morph becomes important when food is less abundant and the plants become crowded, allowing colonization of new plants[95]. Clonal colonies of the rosy-apple aphid display different phenotypes — large and light-coloured, intermediate, and small and dark-coloured — and these phenotypes were shown to correlate with the lack of viruses, the presence of an RNA virus (rosy-apple aphid virus; RAAV) and the presence of a DNA virus (Dysaphis plantaginea densovirus; DplDNV), respectively[96]. Aphids that were co-infected with RAAV and DplDNV were more similar in phenotype to DplDNV-infected insects. The viruses were horizontally rather than vertically transmitted, using the plants as vectors[96], as had been described previously for another aphid virus[97]. Infection with DplDNV had two additional effects on the aphids: reduced fecundity and increased production of the winged morph; these effects did not occur with virus-free aphids or those infected with only RAAV, even under crowded conditions. Hence, DplDNV-infected aphids could grow wings and colonize new plants, but their progeny were not all infected with the virus, so the uninfected progeny could establish rapidly expanding wingless colonies on uninfected plants[96], in another example of a conditionally mutualistic symbiosis.

Aphid–bacterium–virus symbiosis. Aphids harbour several kinds of symbiotic bacteria that have different mutualistic effects. Some bacteria provide nutritional support by producing essential nutrients that the aphids lack. In the pea aphid, the mutualistic bacterial symbiont '*Candidatus* Hamiltonella defensa' provides protection against a parasitic wasp. In aphids without the bacterial symbiont, the wasps lay their eggs in the haemocoel, eventually killing the aphid. The bacteria protect the aphid by producing a toxin that kills the wasp larvae. Recently, it was demonstrated that the toxin is actually produced by a phage of '*Ca*. Hamiltonella defensa' (REFS 98,99). Thus, the aphid provides a snug environment for the bacterium, the bacterium hosts the phage, and the phage produces a toxin that protects the aphid from parasites, so this three-way interaction benefits all of the participants. Nature undoubtedly contains many similar examples of complex mutualistic symbioses, but the complexity of these relationships makes them difficult to tease apart.

Haemocoel
In arthropods, the space between the organs through which haemolymph circulates.

Phages and virulence

Many pathogenic bacteria produce a wide range of virulence factors that help them infect their hosts. There are numerous examples of such virulence factors that are expressed not from the bacterial genome but from a phage genome (reviewed in REFS 100,101). These include: toxins such as diphtheria toxin, which allows *Corynebacterium diphtheriae* to invade the throat tissue of humans, Shiga toxins, which allow normal gut bacteria such as *Escherichia coli* to become invasive, and cholera toxin, which converts non-pathogenic *Vibrio cholerae* into a pathogen that can invade the human gut; proteins that change the antigenicity of pathogens such as *Neisseria meningitidis* or *Salmonella enterica*, allowing these species to avoid the host immune response; and enzymes that allow the bacteria to survive outside the host cell, such as superoxide dismutases in enteric bacteria[101]. These factors may be thought of as pathogenicity factors from the human perspective; from the bacterial perspective, however, they are beneficial, and the phages that produce them are clearly mutualists. Moreover, the study of the viruses in the human gut microbiome is in its earliest stages[102], but undoubtedly we will find that many of the beneficial effects of the microbiome are encoded by viruses. Finally, marine cyanobacteria also harbour phages, and the virus known as S-PM2 encodes two proteins that are components of photosystem II, a major light-harvesting reaction centre in these bacteria. These proteins protect the cyanobacteria from photo-inhibition, a common problem for light-harvesting organisms that occurs when the light is too intense[103].

Conclusions

In spite of the common perception of viruses as pathogens, many viruses are in fact beneficial to their hosts in various ways. There is significant evidence that they have played a major part in the evolution of life on earth. In some cases, viruses have been responsible for major evolutionary leaps, such as the establishment of placental mammals. Some viruses — the polydnaviruses of parasitoid wasps, for example — are required for the survival of their hosts. Some provide a benefit only under certain environmental conditions. Others have allowed the rapid adaptation of their hosts to extreme changes in the environment, which could be increasingly important in the future as we face changes to the Earth's climate. It is likely that many more examples of mutualistic viruses will be discovered in the coming years, especially if researchers open their minds to the possibility that viruses are not all bad.

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Competing interests statement
The author declares no competing financial interests.

FURTHER INFORMATION
Marilyn Roossinck's homepage:
http://www.noble.org/PlantBio/Roossinck/index.html

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