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Living with the enemy: viral persistent infections from a friendly viewpoint

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Persistent infection is a situation of metastability in which the pathogen and the host coexist. A common outcome for viral infections, persistence is a widespread phenomenon through all kingdoms. With a clear benefit for the virus and/or the host at the population level, persistent infections act as modulators of the ecosystem. The origin of persistence being long time elusive, here we explore the concept of 'endogenization' of viral sequences with concomitant activation of the host immune pathways, as a main way to establish and maintain viral persistent infections. Current concepts on viral persistence mechanisms and biological role are discussed.

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Introduction

Since the discovery of the first virus, Tobacco Mosaic virus, in 1892 there has been continuous interest in understanding virus–host interactions. Almost all of the studies addressing these interactions are based on deleterious or pathogenic viruses with an obvious medical or agricultural impact. Nowadays, thanks to the advent of new techniques such as next generation sequencing, new windows are being opened in our understanding of viruses and their effects on the host. In general terms, infections can be grouped into two categories, regardless of the infecting agent (virus, viroid, bacterium, fungus or any parasite in general) or the host (bacteria, fungi, plants, and animals): firstly, acute, or secondly, persistent (comprising latent or chronic infections, and a particular case for mutualistic infections). A virus acute infection is characterized by a high viral replication rate and the production of a large number of progeny. Replication is transient in an individual host, as it is limited either by the death of the host (and/or cells inside the host) or by the host immune responses. A persistent infection lasts for longer periods of time and may be the result of an acute primary infection that is not cleared. In this case, the ability of the virus to be transmitted to other organisms or offspring of the host is maintained. Within this group, a latent infection involves periods, sometimes extensive, in which the host produces no detectable virus. In contrast, a chronic infection produces a steady level of virus progeny. Mutualistic infection is less known and characterized, but may be one of the most widespread kinds of infection. In such kinds of infection, viruses have a positive effect on the host. In a general manner, these interactions are durable in time and in many cases the viruses have been adopted by the host (endogenous virus) [1,2••,3,4].

Although the boundaries between these different kinds of infections are sometimes blurry, in this review we will focus on persistent infections and their repercussions on the host.

Persistent infection throughout the different kingdoms

Persistent infection seems to be a common outcome in nature, partly because of the positive effects of parasites under some conditions [5,6••]. It has been proposed that asymptomatic infections could contribute to resistance to further infection [7•,8]. It has also been proposed that emerging viruses such as HIV [9], SARS [10] or influenza [11] have ancestors that are not pathogenic; rather, they are persistent or endemic viruses in other hosts. In this context it is tempting to think of viruses as modulators of the ecosystem. For instance, farmed animals and plants are frequently plagued with disease-causing or lethal virus infections. The lack of heterogeneity in the host population, together with the overcrowding of individuals, may create conditions where the asymptomatic virus can switch to an acute infection. This infection may then force the appearance of less susceptible host variants or may reduce the host population to a size that can no longer support viral transmission or dissemination. In both cases, even when the acute infection has a cost for some or many individuals, the host population may gain benefits at the species level.

A persistent infection could be considered as the most well-adapted or successful host–pathogen interaction. From a viral standpoint, persistence has benefits at different levels:

(i) A persistent infection allows virus production and assures the transmission of viral genetic material over a longer period of time.

(ii) Because there is low or no fitness cost to the host, a persistence state could permit multiple infections (with the same or different viruses) that could be the source of new genetic variability and complexity.
(iii) Since the host's health is not significantly affected, at least in the short term, a mobile host can disseminate virus to more hosts within the same environment or to hosts in a new environment.

From a host standpoint, persistence is profitable because:

(i) Persistently infected organisms are resistant to super infections with related viruses, a phenomenon known as viral accommodation [12].
(ii) Persistently infected populations (such as mice) can carry and transmit viruses to sensitive populations and eventually settle and/or replace them (i.e. mice haystack colonization [13]). In this way, the persistently infected original population can establish in a new area.
(iii) Organisms persistently infected with mutualistic viruses show an increased antiviral response [14,15].
(iv) Mutualistic viruses can help the host by supplying new genes or through epigenetic changes of the host genome with beneficial results [16].

Examples of persistent infection can be found in almost all the organisms (Table 1). Below are summarized some examples:

- The close relationship between bacteria and lysogenic phages is very well documented. Lysogeny typically results in bacterial resistance to infection by homologous or related phages. Even if phages are not continuously replicating, the viral genomes are always present in the host, in many cases providing advantages for colonization [17,18•], for example during the competition for a new niche. Other related situation is the phage production of toxins such as Shiga toxins that allow nonpathogenic gut bacteria to become invasive (for more examples see review [19]).
- Viral infections in fungi is a particular and almost extreme case of persistent infection, since mycoviruses have lost the extracellular phase of their viral replication cycle, and as a consequence, depend on the host for transmission. Viral infected fungi can infect plants as described by Marquez *et al.* [6••]. In this threesome, *Curvularia protuberance* (a fungus) confers heat tolerance to the plant *Dichanthelium lanuginosum* through the presence of the mycovirus *Curvularia thermal tolerance virus* [6••].
- Viruses belonging to the *Partitiviridae* family and the *Endormavirus* genus can establish persistent infections in plants. One illustrative example is the blueberry latent virus (BBLV), a dsRNA virus that is present in more than 50% of blueberry crops in the United States [20]. The presence of BBLV was originally associated with the blueberry fruit drop disorder, but the virus is widespread in symptomatic as well as asymptomatic plants. Asymptomatic plants carrying the virus were followed for several years and never showed signs of the disorder [20].
- Fish also carry persistent infections, as represented for the salmonids species carrying the infectious pancreatic necrosis virus (IPNV). IPNV can produce an acute, systemic infection that results in high mortality in farmed salmonids, and a persistent infection associated with resistance to super infection in surviving fish after outbreaks [21].
- Mammals are also persistent viral carriers. For instance, humans support eight types of prevalent, persisting herpes viruses without a clear fitness cost to individuals. Interestingly, these interactions are highly species specific, since one of these viruses (human herpesvirus type 1) is known to produce lethal infections in ape colonies [22]. Another example is the simian immunodeficiency virus (SIV) that infects more than 40 species of African nonhuman primates. In several of them, such as African green monkeys, the infection is nonpathogenic despite a chronically high viremia [23]. However, when Asian macaques are infected with SIV, they develop AIDS. Interestingly, SIVs from African nonhuman primates are the ancestors of HIV-1 and HIV-2 [23].

In summary, all host species have developed different strategies to control viral infection (i.e. CRISPR in bacteria and archaea, plasmid exclusion system in bacteria, RNA interference (RNAi) in plants, arthopods and nematodes, adaptive immunity in vertebrates, among others) and viruses have counter-attacked ensuring their survival and transmission by developing a myriad of circumventing defense mechanisms. For instance, HIV-1 does not induce IFN during infection [24] and insects and plants viruses developed viral suppressors of RNAi to avoid the RNAi antiviral response [25]. Regardless of the complexity of these relationships, in all kingdoms we can find situations where the antiviral mechanism is used to reach a metastable equilibrium: the persistent state.

Persistent infection in arthropods

Among animals, arthropods have been present on earth from the early Cambrian period of the Paleozoic era and will likely continue for millions of years to come. We can hypothesize then that arthropods are better adapted to viral infection than mammals because the interaction is much older. Actually, it is well documented that arthropods coexist with persistent viral infections without fitness cost for the host. Thus, one could view

Table 1

Viral persistent infections across kingdoms

Host	Virus	Viral family	Viral Genome	Comments	Refs
Bacteria					
Corynebacterium diphtheriae	Phages β and ϖ	Siphoviridae (β)	dsDNA	First phage exotoxin characterized	[19,36]
Escherichia coli	933W and H19B	Podoviridae (933W) Siphoviridae (H19B)	dsDNA	Two different phages coding for Shiga toxins	[19,36]
Vibrio cholerae	ctxϕ	Inoviridae	(+) ssDNA	Phage coding for Cholera toxin	[19,36]
Salmonella enterica	sopEϕ GIFSY-2 GIFSY-3	Myoviridae (sop) Siphoviridae (GIFSY)	Linear dsDNA	Phage protein involved in cellular invasion	[36]
Mycoplasma arthritidis	Mycoplasma arthritidis virus 1	Unclassified dsDNA phages	Linear dsDNA	Phage adhesion protein for bacterial host attachment	[36]
Fungi					
Cryphonectria parasitica	9B21	Reoviridae	Segmented dsRNA	Virus reduces fungus virulence	[37]
Curvularia protuberance	Curvularia thermal tolerance virus	Unclassified	Bi-segmented dsRNA	Virus infected fungus confers heat tolerance to plants infected with the fungus	[6••,38]
Plants					
Cannabis sativa	Cannabis cryptic virus	Partitiviridae	Bi-segmented dsRNA	Asymptomatic widespread hemp virus. Seed-transmissible	[39]
Vaccinium spp.	Blueberry latent virus	Partitiviridae	dsRNA	Asymptomatic	[20]
Nicotiana benthamiana	Cucumber Mosaic virus	Bromoviridae	(+) ssRNA	Virus confers drought tolerance	[40,41]
Animals					
C. elegans	Orsay virus	Nodaviridae	Bi-segmented (+) ssRNA	Virus cause damage in intestinal cell, with little impact on the whole organism	[42]
Macrobrachium rosenbergii	White spot syndrome virus	Nimaviridae	dsDNA	Virus-challenged shrimp larvae remain infected for life without signs of disease	[43]
Aedes aegypti	Rift valley fever virus	Bunyaviridae	(−) ssRNA	Virus enhance ability of mosquito to find blood vessels	[14]
Drosophila spp.	Drosophila C virus	Dicistroviridae	(+) ssRNA	Infected adult flies get a boost in reproduction	[14]
Salmo salar	Infectious pancreatic necrosis virus	Birnaviridae	Bi-segmented dsRNA	Viral infected survivor salmons are protected against future disease	[44]
Clupea pallasii	Chronic viral hemorrhagic septicemia virus	Rhabdoviridae	(−) ssRNA	Viral infected survivor herrings are protected against future disease	[8]
Meleagris gallopavo	Turkey hemorrhagic enteritis virus	Adenoviridae	dsDNA	Avirulent strain produce persistent infection and is used as a live-virus vaccine	[45]
Miniopterus magnate	Bat-CoV 1A	Coronaviridae	(+) ssRNA	Asymptomatic	[46]
Mus musculus	Lymphocytic choriomeningitis virus	Arenaviridae	Segmented (−) ssRNA	Specific viral sequences persist as DNA forms	[15,33]
Homo sapiens	Coxsackie virus B4	Picornaviridae	(+) ssRNA	Virus could increase or prevent diabetes risk	[47]
Homo sapiens	Herpes simplex virus	Herpesviridae	Linear dsDNA	Virus establishes latent infection in sensory neurons	[41]

persistent infection not as a defect in the antiviral response, but as part of arthropod immunity. In this context, we can consider that persistent infection had been selected as a strategy of survival. In absence of a conventional immunological memory (through antibodies), arthropods have found, in the establishment of persistent infections, a way to control and lower viral replication. This mechanism is useful and essential to survive new and more aggressive infections [26].

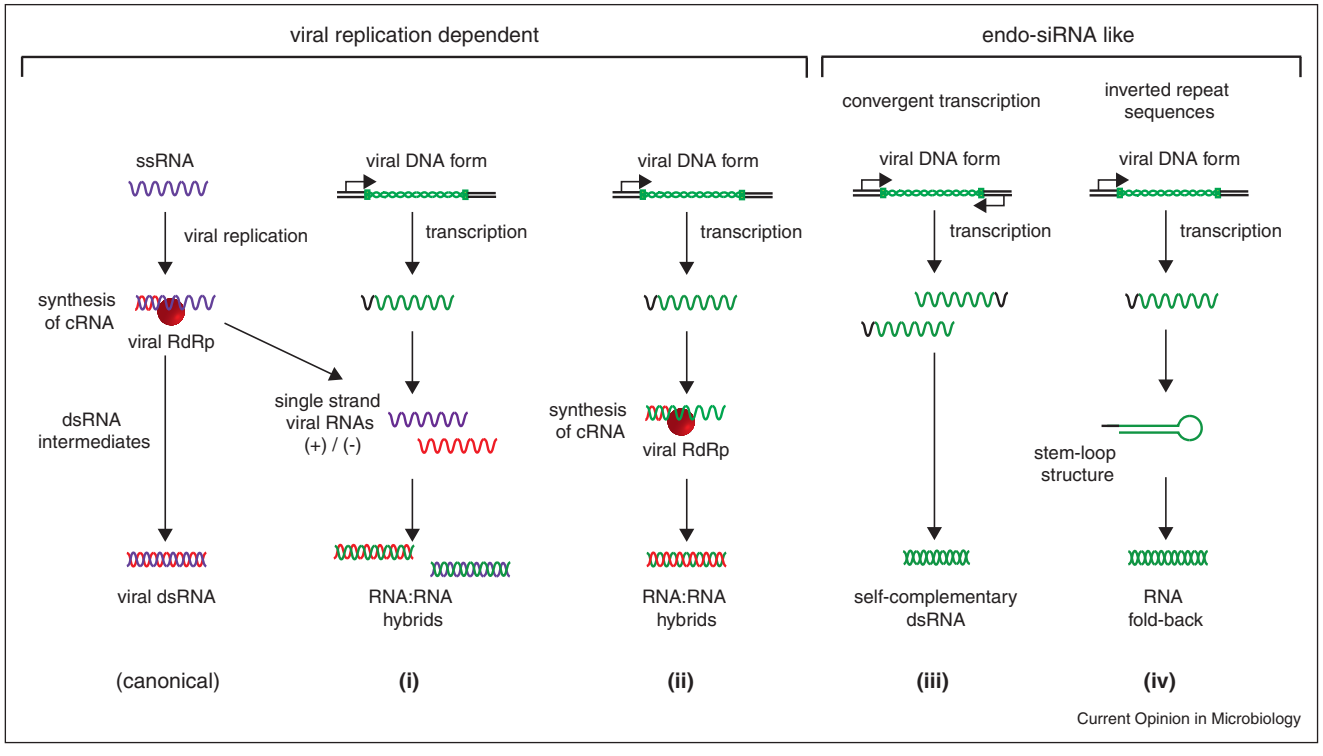
The most well-known persistent infections are the arthropod/arbovirus interactions, probably because of the direct effects on human health and economy. Arboviruses (arthropod-borne viruses) are a group of viruses belonging to different families that are transmitted by arthropod vectors, mainly of the mosquito and tick families. Among the most common arboviruses we can mention dengue virus, sindbis virus, yellow fever virus, chikungunya virus, Rift Valley fever virus, La Crosse encephalitis virus, and West Nile virus.

Role of endogenization of viral sequences in the establishment of persistent infection

The host–pathogen interaction triggers selection pressures in both organisms that constantly need to evolve in order to adapt. This adaptation sometimes implies endogenization of the full parasitic organism, as is the case of the endosymbiont bacterium *Wolbachia* that protects fruit flies and mosquitoes against several viral infections [27,28,29••] and in other cases, just a part of the parasite genome. This endogenization can be a rapid source of variability comparable to that of transposable elements. For the latter, it was shown that during Sigma virus infection in *Drosophila*, transposons insert into different genomic locations, disturbing protein gene expression and leading to an increased viral resistance [30], showing that changes to the genetic makeup of the host can be helpful and relatively quick in producing pathogen resistance. During population evolution, the appearance of spontaneous mutations with a positive effect on adaptation is a very slow process when compared to the effects of endogenization of parasites and/or transposition triggered by the presence of the parasite.

In the last decade, several works have shown the 'endogenization' of viral genomes belonging to nonretroviruses in several different species [1,2••,4,15,31,32]. It is tempting to propose that nonretroviral DNA endogenization is actively involved in antiviral immunity because of three main lines of evidence: firstly, studies in bees (*Apis mellifera*) have shown that an important percentage (more than 30%) of the insect population carries a segment of the Israeli Acute Paralysis Virus (IAPV) ((+) ssRNA) in their genome and this subpopulation became virus resistant [32]; secondly, nonretroviral DNA sequences with a potential role on immunity have also been described in mammals [15,33]. In the case of lymphocytic choriomeningitis virus (LCMV), the acquisition of some parts of the viral genome by spleen cells is correlated with the maintenance of viral antigens (i.e. specific antibodies). Interestingly this DNA form was produced only in the natural host [15], reinforcing the idea that persistent infections play a role in the modulation of the immune system; thirdly, arbovirus-derived piRNAs have recently been detected in mosquitoes [34•,35•]. Cellular piRNAs, derived from only one of the DNA strands have been linked to both epigenetic and post-transcriptional gene

Figure 1



Hypothetical involvement of endogenized viral DNA in RNAi-mediated antiviral defense. Viral dsRNA is the danger signal that triggers the antiviral RNAi response. It is commonly accepted that during viral replication, dsRNA molecules (canonical) are produced and they are the substrate of Dicer. Whether DNA from viral origin is involved in a RNAi response remains to be confirmed. However, one could postulate a role of the endogenized viral DNA in antiviral response through the production of different molecules of dsRNA (i–iv). Some of these molecules could involve the viral RdRp (i and ii) while others could be reminiscent of endo-siRNA biogenesis (iii and iv).

silencing of retrotransposons and other mobile elements. The source of viral-derived piRNAs and their biogenesis remains uncharacterized. We could then hypothesize that in insects, and maybe in other organisms, DNA from nonretroviral RNA viruses is produced, endogenized and boosts the antiviral response under the form of viral siRNA or viral piRNAs derived from a transcript processed from that same DNA.

Until now parasite DNA endogenization has been considered as a rare event, since it has been assumed that only endogenization on the germ line has an effect (positive or negative). However, somatic or 'nontransmissible endogenization' may be much more frequent than expected, since the integrity of the genome in the soma could be more relaxed. In this context, it is tempting to postulate that this somatic endogenization helps in the control of viral infection by the same mechanism that transposons are controlled, that is, endo-siRNA or other RNAi related pathway. This system could be of particular interest contributing, for example, to the priming or to the acquisition and maintenance of a systemic immunity.

Interestingly, this hypothesis postulates that these DNAs from viral origin should be involved in dsRNA biogenesis in order to trigger small RNAs-mediated immunity. Several different sources for the dsRNA other than viral dsRNA from replication intermediates that triggers the RNAi response can therefore be possible (Figure 1): firstly, a single-stranded viral transcript generated from the DNA form would anneal to the viral genome (either the (+) or the (−) strand depending on the orientation of the transcript); secondly, a single-stranded viral transcript generated from the DNA form would be template for the viral RNA-dependent RNA polymerase (RdRP) generating dsRNA that will trigger the siRNA pathway; thirdly, two complementary single-stranded viral transcripts generated from different loci or by convergent transcription; fourthly, a single-stranded viral transcript generated from the DNA form would fold back on itself forming secondary structures (dsRNA) that could be recognized by the RNAi pathway, similar to endo-siRNAs. It is still unknown whether these new DNA molecules of viral origin are heritable or not and whether this mechanism is universal. However, in a process that strikingly recalls the canonical adaptive immune response in mammals, this acquired DNA could improve the 'innate' antiviral response of the host sufficiently enough to guarantee the survival and reproduction of the host and therefore, the viral propagation. Finally, we could consider the endogenization mechanism as an alternative view of immune memory (protection from a secondary exposure to the same 'antigen'). Despite the absence of specialized memory immune cells in plants and invertebrates, there is a 'DNA memory' that would allow a rapid response, limiting pathogen proliferation and spread.

Closing remarks

Our knowledge about viruses is biased, mainly because of the evident and urgent need to understand and control harmful viruses. Nevertheless, more and more evidence is emerging of a friendlier coexistence and coevolution between viruses and hosts. The sequencing age has brought to light that many viruses or parts of them (whether retroviral in origin or not) are integrated into the hosts' genome. A majority of these sequences are remnants of ancient virus infections, analogous to scars or fingerprints. These remnants present in all species are not just the result of a random event and force us to rethink how we understand and conceptualize viral infections. Nowadays we are becoming aware of the thousands of viruses among us, but only few of them have a negative, albeit considerable, impact. In this case, deciphering the mechanism(s) by which the delicate equilibrium between viruses and hosts is maintained, may serve as a guide for controlling deleterious acute infections in the future.

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