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Within host RNA virus persistence: mechanisms and consequences

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Abstract

In a prototypical response to an acute viral infection it would be expected that the adaptive immune response would eliminate all virally infected cells within a few weeks of infection. However many (non-retrovirus) RNA viruses can establish "within host" persistent infections that occasionally lead to chronic or reactivated disease. Despite the importance of "within host" persistent RNA virus infections, much has still to be learnt about the molecular mechanisms by which RNA viruses establish persistent infections, why innate and adaptive immune responses fail to rapidly clear these infections, and the epidemiological and potential disease consequences of such infections.

Introduction

Infections with most non-retroviral RNA viruses cause characteristic signs and symptoms of an acute disease. During the acute phase of infection, the virus replicates rapidly and is shed into the environment with spread to new susceptible individuals. Recovery is typically associated with virus clearance and establishment of varying lengths of immunity to re-infection. For such viruses to be maintained within a population there needs to be a continuous supply of susceptible individuals to sustain the transmission cycle. For viruses, other than endogenous retroviruses and viruses transmitted vertically, if the host population size and/or density is small, as was likely the case during most of human evolution and is currently the situation for many animal populations, the number of susceptible individuals may not remain high enough for the virus to maintain itself within a host population. Conversely, if the population density is very high, for example in bat colonies, virus spread may be extremely rapid thereby also leading to a decrease in the numbers of susceptibles (through the induction of long-lasting protective immunity [1] and/or through high mortality rates) to levels below that required for continued virus transmission [2]

This opinion piece takes its title from a conference with the same name that was held in St Andrews, Scotland on 24th – 26th August 2016

Because viruses are obligate intracellular parasites that must be maintained in a population, RNA viruses have evolved a number of strategies to counteract the potential problem of "running out" of susceptible individuals, such as: i) a high mutation rate that results in ongoing immune selection of antigenic variants (*e.g.* influenza virus), ii) infection of mucosal surfaces, where it is difficult to induce long lasting protective immunity, resulting in repeated infections with the same virus (*e.g.* respiratory syncytial virus) or iii) infection of multiple species, thereby increasing the numbers of susceptible individuals. As an additional strategy some viruses, such as hepatitis C virus (HCV) and Borna disease virus (BDV), have evolved specific mechanisms that lead to the establishment of persistent infections in at least some individuals who can then act as reservoirs for the virus within a host population.

In a prototypical response to an acute viral infection it is expected that a virus will be cleared by innate and adaptive immune responses within a few weeks of infection. Therefore, any infection that persists longer than this may be considered persistent, even if it does not lead to life-long infection with the production of infectious virus. Indeed, for foot and mouth disease virus (FMDV), cattle are considered persistently infected if infectious virus can be detected for more than 28 days after infection [3,4]. Not all persistent infections may represent a selective advantage for a virus. Thus viruses, or viruses with defective genomes, may persist and slowly spread from cell to cell without the production of infectious virus. Such infections may nevertheless have important consequences for the host in that they may lead to chronic or even fatal disease outcomes, for example persistent measles virus (MeV) infections of the brain can lead to subacute sclerosing panencephalitis (SSPE) [5,6], or they may induce life-long immunity thereby preventing reoccurrence of the acute infection, as has been suggested for MeV [7]. It is this broad definition of persistence that we will take in this opinion piece as we consider some of the outstanding issues regarding "Within host RNA virus persistence".

Epidemiological consequences of persistent infections

The ability of some RNA viruses, e.g. HCV and BDV, to establish persistent infections in a significant proportion of infected hosts is critical for them to be maintained within their host communities. However, the importance of persistent infections for the epidemiology of other viruses has yet to be established (Table 1), particularly those that cause acute infections with obvious clinical outcomes. However, the example of FMDV is instructive. Although FMDV is best known for causing devastating outbreaks of acute disease in domesticated ungulates (*e.g.* cows and sheep), it can also establish persistent infections in some animals (persistently infected sheep and goats can shed virus for up to 9 months, cattle for up to 2.5 years and buffalo for >5 years) which can act as a source of FMDV in future outbreaks [3,4]. Similarly, swine vesicular disease virus may be able establish persistent infections in pigs (>100 days) that may act as carriers of swine vesicular disease [8]. There is also evidence that acute respiratory viruses, such as rhinoviruses [9,10] and respiratory paramyxoviruses [11], establish persistent infections in some individuals with production of infectious virus for many weeks or months, although such infections are often, but not always, associated with immune dysfunction (see below) and/or age. Also, whilst many arboviruses are able to establish inapparent life-long persistence in their arthropod vector [12], they often cause significant acute disease in their vertebrate hosts, although their ability to establish persistence in vertebrates may have been under-estimated [13].

Even such obviously acute virus infections such as Zika virus and Ebola virus in humans can persist in very small numbers of individuals over a period of months, and perhaps years, and such persistently infected individuals can occasionally transmit the virus, thereby being a potential source of future outbreaks [14,15]. Whilst no one would suggest that the ability of Ebola virus to establish persistent infections has evolved in humans, the fact that even small numbers of individuals can become persistently infected may reflect its intrinsic ability to establish persistence in its natural host.

One potential advantage of persistent infection for the infected host may be the maturation of the antiviral immune response and development of long-lasting protective immunity. For instance, persistence of measles virus RNA and protein in lymphoid tissue for months after the primary infection stimulates continued production of plasmablasts producing MeV-specific antibody of increasing avidity, T cells of evolving functionality and the establishment of life-long immunity that characterizes recovery from measles [16,17]. Thus, there may be clear advantages both for the virus and host in evolving towards the establishment of persistent infections, especially because virus:host interactions that result in persistent infections are unlikely, in most cases, to lead to high levels of mortality.

Disease consequences of persistence

Although most persistent RNA virus infections are probably inapparent, persistent infections can sometimes lead to chronic disease or relapses of acute disease. Long-recognized examples include hepatocellular carcinoma and liver fibrosis as a late consequence of HCV infection[18], and SSPE following measles virus infection. Indeed, the CNS, as an immunologically privileged site (see below), is an organ in which RNA viruses can often establish persistent infections with disease consequences [5,19]. Recent examples include reactivation of CNS infection after apparent recovery from Ebola virus disease [14,20]. Other chronic human diseases have also been linked to persistent RNA virus infections, some controversially, include Paget’s bone disease, multiple sclerosis, otosclerosis, post-polio syndrome and other late neurodegenerative diseases, chronic fatigue syndrome, certain autoimmune diseases and exacerbation of chronic obstructive pulmonary disease. (Table 2)

Mechanisms of persistence

To establish persistent infections viruses must i) avoid elimination by the host’s immune response, and ii) avoid killing all infected cells whilst maintaining their genomes within some infected cells. This may entail low level virus replication within cells that themselves remain persistently infected (e.g. BDV), infections in which the virus slowly spreads from cell to cell, but during which the infected cells may die (e.g. rabies virus), or infections in which the virus passively hides without apparent replication (e.g. BTV in erythrocytes [21–23]). Both viral and host factors will influence the type of persistent infection established. For viruses that clearly need to establish persistent infections to survive in nature the molecular basis by which they do so must be an evolved process. However, this is unlikely to be the case for viruses where the establishment of persistence has no obvious selective advantage for the virus, unless the general way the virus replicates reflects the need of an ancestral virus to establish persistent infections, or the virus establishes advantageous persistent infections in a different host.

Repression of virus transcription and replication

If a cell continues to synthesize high levels of viral proteins, the cell will probably die either as a direct consequence of virus replication or be eliminated by innate and adaptive immune responses. Therefore, to establish persistent infections virus replication probably needs to be repressed in at least some infected cells. Long-lived cells such as cardiac myocytes and brain and spinal cord neurons may be particularly likely to restrict virus replication and avoid immune-mediated elimination (see below). However, RNA viruses can establish persistent infections in a variety of tissues, not all of which are immune privileged sites. How repression of virus replication is achieved in these cells, even for a well-studied virus such as HCV, is usually not clear. HCV appears to have evolved mechanisms to hijack cellular factors, such as microRNAs that bind its genome to protect it from degradation by the 5′–3′ exoribonuclease Xrn1[24], inhibit its detection by sensors of the innate immune response and to regulate virus transcription, replication and genomic RNA abundance [25]. BDV, linked to neurobehavioral disorders, is the only member of the order Mononegavirales that replicates in the nucleus and non-cytolytically infects animals to establish persistence [26]. To maintain persistence, BDV tethers its genome to host cell chromosomes, so that both daughter cells remain infected when the cell divides [27]. BDV also blocks apoptosis, and thus promotes persistence by preventing cell death, through the action of its accessory protein X [28], which may influence the establishment and reactivation of BDV through its regulatory function on virus polymerase activity [29]. Furthermore, 5′-terminal trimming, a mechanism that leads to the loss of terminal nucleotides from the BDV genome, may attenuate virus replication and transcription (thereby also helping to facilitate virus persistence), and prevent the genome from activating innate immune responses, which also strongly influence the outcome of virus infections (see below) [30]. Similar modifications (deletions and insertions) at the 5′ and/or 3′ ends of the genomes of other RNA viruses, including LCMV, hantaviruses and coxsackieviruses [31–33], may also play similar roles in influencing their ability to establish persistent infections. Certain insect and plant viruses also appear to have evolved mechanisms, dependent upon the insect's siRNA defense system, to dampen down their replication thereby facilitating virus persistence. Here, viral dsRNA produced during virus replication is recognized by Dicer-2 (DCR2), a central component of the siRNA pathway, that processes the RNA to produce virus-derived siRNAs. These are subsequently recognized by the RNA-induced silencing complex (RISC) resulting in the specific cleavage viral mRNA, thereby inhibiting lethal, acute infections and virus persistence in the insect vector [34,35]. The siRNA defense system may also suppress the replication of mammalian arboviruses in their insect vectors to levels that favour the establishment of persistence and the survival of the vector [36] However, it is not known whether other RNA viruses, such as certain paramyxoviruses, that can establish persistent infections have also evolved specific mechanisms to down regulate virus transcription and replication under certain conditions. Nevertheless, it is interesting to speculate that the reason some viruses can establish persistence in their natural hosts but cause serious disease in other species (e.g. hantaviruses [37,38], or possibly even Ebola virus), is because the mechanisms they have evolved to dampen replication in their natural hosts do not function in other species.

It is unlikely that highly cytocidal viruses will be able to establish persistent infections unless either some infected cells are restrictive or semi-permissive for virus replication, or virus variants, including temperature sensitive mutants [39], with reduced cytopathogenicity are selected during the establishment of persistent infections. Such an outcome is much more likely for RNA viruses than DNA viruses given the high mutation rate of RNA viruses and their quasispecies nature [40–43]. Similarly, the presence and amplification of defective interfering particles may also dampen virus replication and thus influence the establishment of persistence [44–46]. A rare way to establish RNA virus persistence, that is unlikely to be of evolutionary benefit to the virus, is the production of a cDNA copy of the viral RNA by endogenous reverse transcriptase, as has occurred for BDV and been proposed for measles virus and LCMV [47–50].

One general way for viruses to restrict replication is through limited activation of the interferon (IFN) response. This is an extremely powerful antiviral response that has co-evolved between virus and host for millions of years and is a programmed response that plays an essential role in controlling many virus infections. Regulation of this innate response plays a role in persistent hepatitis A infection of hepatocytes [51] and arbovirus infection of mature neurons [52]. There is also evidence that, for some viruses, variants that induce IFN, or are relatively sensitive to IFN, may be better able than the wild type viruses to establish persistent infections [53,54].

Interaction with the immune system

A major host factor that profoundly influences the establishment of persistent infections is the competence of the immune response and patients with immunodeficiencies in innate, adaptive, or combined immune responses are susceptible to development of persistent and progressive infections with attenuated as well as wild type RNA viruses. As examples, in addition to progressive disease in severely immunodeficient children [55], children with defects in the IFN response cannot rapidly clear the attenuated viruses included in the measles-mumps-rubella (MMR) vaccine, despite having an apparently normal adaptive immune response [56,57]. Polymorphisms in the IFN-lambda response has been reported to influence the outcome of HCV and its ability to establish persistent infections [58]. Individuals with an inability to make immunoglobulins (agammaglobulinemia) can become persistently infected with a variety of RNA viruses, including echoviruses, enteroviruses, rhinoviruses and parainfluenza viruses [11,59–61]. Furthermore, immunodeficient individuals persistently infected with poliovirus are a challenge for the WHO’s vaccination campaign to eradicate poliomyelitis [62]. Indeed, given our advances in how to treat autoimmune disease with immunosuppressive drugs and the survival of patients with immunodeficient disorders, such individuals, if they become persistently infected, may become significant reservoirs for some infectious diseases and nosocomial infections.

To establish persistent infections in immunocompetent individuals, viruses must avoid elimination by a fully functional immune system, including innate and adaptive responses.

With regards innate responses, these include avoidance of elimination by apoptosis [63] and the interferon (IFN) response. IFNs are cellular factors produced by infected cells that interact with receptors on infected and uninfected cells to induce expression of antiviral proteins that restrict virus replication. Indeed, to survive in nature all viruses must at least partially circumvent the host IFN response and to do so they often hide, or modify their genomes, such that they do activate the IFN system, and/or produce proteins that act as IFN antagonists [64]. The mechanism by which these IFN antagonists work potentially has a strong influence on the ability of viruses to establish persistent infections. Some lytic viruses (e.g. alphaviruses in vertebrate hosts) block the IFN response by inhibiting cellular transcription or protein synthesis, which inevitably leads to cell death. Therefore, for reasons discussed above, it is likely that non-cytolytic variants will evolve during the establishment of persistent infections. Other RNA viruses by nature are less lytic, and produce IFN antagonists that allow cell survival and promote the establishment of virus persistence. Indeed, the mechanisms of action of such viral IFN antagonists may have specifically evolved to facilitate persistence.

To establish persistence viruses must also avoid elimination by antibody and T-cell responses, and this may necessitate the down-regulation of virus protein synthesis and replication (see above). Viruses may also establish persistent infection in immunologically privileged sites such as the brain or testis [5,65,66] and, although the brain is likely to be a dead-end organ for the most viruses, testicular infections can facilitate transmission [66–69]. The likelihood of persistence can also be influenced by the promptness of the virus-specific antibody response and relative timing of the appearance of populations of effector and regulatory T cells. Viruses may be more likely to persist if the effector response is suppressed prior to clearance or if infection occurs at a very young age and immunologic dysfunction/tolerance is established (e.g. bovine viral diarrhea virus infection in cattle, congenital rubella in humans, LCMV in mice) [70–72]. Viruses can also suppress development of the adaptive antiviral immune response and promote persistence by replicating in cells and tissues of the immune system [73,74]. For instance, bluetongue virus, an arthropod-borne reovirus, infects and destroys follicular dendritic cells in germinal centers of lymph nodes and prevents prompt development of antibody capable of clearing infection [75]. Conversely it has also been suggested that an inappropriate antibody response may facilitate persistence, as has been suggested for measles and Junin virus infections [76,77]. How this may work is an open question, but antibody-induced antigenic modulation can reduce the level of measles viral glycoproteins on the surface of persistently infected cells below that required for lysis by antibody-dependent cellular cytotoxicity (ADCC), a mechanism by which cytotoxic cells target virus-infected cells [78]. Furthermore, antibodies against the measles virus haemagglutinin can also reduce the expression of viral proteins within cells, thereby potentially preventing cell death and reducing the likelihood of the cells being killed by the immune response [79,80].

To conclude, despite the fact that persistent RNA virus infections can have important consequences both for the virus and host, much has still to be learned about “Within host persistent RNA virus” infections. With the advent of new technologies, such as next generation sequencing, the tools are now available to better study persistent infections both *in vivo* and *in vitro*. Such studies may be used to investigate possible associations of persistent virus infections with chronic human diseases. A better understanding of the incidence and nature of persistent RNA virus infections may also promote development of better methods for surveillance and control; for example, it may be possible to design improved vaccines using viruses that establish persistent infections as vectors to induce long lasting immunity.

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Highlights

1. Persistent infections as reservoirs of infection and RNA virus epidemiology
2. Disease and immune consequences of persistent RNA virus infections
3. The role of host responses and virus mechanisms in the establishment of persistent infections

Table 1

Examples of viruses that can establish persistent infections, including in immunocompromised hosts, and some associated references

Arenaviridae, Mammarenaviruses, e.g. lymphocytic choriomeningitis virus [81]
Arteriviruses, e.g. equine arteritis virus, simian haemorrhagic fever virus [82]
Bornaviridae, e.g. Borna disease virus [83]
Bunyaviridae
Hantaviruses [37,38,84]
Caliciviridae
Noroviruses e.g. Norwalk virus [85]
Coronaviridae, e.g. mouse hepatitis virus [86]
Endornaviridae and Partiviridae; [87]
Filoviridae, Ebolaviruses, e.g. Ebola virus [20,68]
Marburg viruses, e.g. Marburg [88]
Flaviviridae
Hepacivuses, e.g. hepatitis C virus [89]
Pegivirus, e.g. GB viruses [90]
Flavivirus, e.g. West Nile virus [91], Zika [15,67], Japanese encephalitis [92], tick borne encephalitis [93]
Pestiviruses e.g. Bovine viral diarrhea virus [70,94,95]
Nodaviridae e.g. flock house virus of insects [35] ([96]
Orthomyxoviridae, e.g. influenza viruses [97,98]
Paramyxoviridae [11]
Morbilliviruses, e.g. measles virus [99], canine distemper virus [100], feline morbillivirus [101,102]
Respiroviruses, e.g. parainfluenza virus type 3 [103]
Rubulaviruses, e.g. parainfluenza virus type 5 [104], porcine rubulavirus [105]
Picornaviridae
Aphthoviruses, e.g. foot-and-mouth disease virus [4]
Cardioviruses, e.g. Theilers murine encephalomyelitis virus [106]
Enteroviruses, e.g. poliovirus [62], coxsackievirus [31], rhinoviruses [9,10], swine vesicular disease virus [8]
Pneumoviridae, e.g. respiratory syncytial virus [107–109]
Reoviridae
Orbivirus, e.g. bluetongue virus [21–23]
Phytoreovirus, e.g. rice gall dwarf virus [34]
Rhabdoviridae
Lyssaviruses e.g. rabies virus [110,111]
Togaviridae
Alphaviruses, e.g. Chikungunya [112]
Rubiviruses, e.g. rubella virus [113]
See also arboviruses [13]

Table 2

Examples of human diseases associated, sometimes controversially, with persistent RNA virus infections and some associated references

Autoimmune diseases: various viruses [114,115]
Chronic fatigue syndrome: enteroviruses [116]
Exacerbation of chronic obstructive pulmonary disease: Respiratory syncytial virus [108]
Liver cirrhosis/cancer; hepatitis C virus [117]
Multiple sclerosis: a number of RNA and DNA viruses [118,119]
Paget's bone disease: Measles and other paramyxoviruses [11,120]
Persistent arthralgia: Chikungunya virus [121]
Post-polio syndrome: polio virus [122]
Progressive rubella panencephalitis; Rubella [113]
Subacute sclerosis panencephalitis and measles inclusion encephalitis: measles virus [123]
Olfactory dysfunction; parainfluenza virus type 3 [124]
Otosclerosis: measles virus [125,126]