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Strength in Numbers: Mechanisms of Viral Co-infection

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Abstract

RNA virus populations are diverse due to a variety of factors, including lack of proofreading of the viral RNA-dependent RNA polymerase. These diverse viral populations include defective viruses incapable of productive infection. Recent studies have determined the existence of several modes of viral transmission outside of canonical pathways, including en bloc transmission of multiple viruses into a single host cell via membrane vesicles. Additionally, it has recently been determined that viral aggregation and bacteria can facilitate the delivery of multiple viruses to a single cell. Co-infection of RNA viruses is important since it has the potential to enhance viral fitness. Furthermore, through complementation and recombination, co-infection could potentially promote "resurrection" of otherwise defective viral genomes and has the potential to expand viral diversity.

Keywords

RNA viruses; Viral Co-infection; Viral Evolution

1. Introduction

1.1. RNA viruses

RNA viruses exist as diverse populations due to the high prevalence of mutations in their genomes (Domingo and Holland, 1997; Drake, 1993). While some mutations can be advantageous, the majority of mutations within viral genomes are neutral or deleterious to the virus. RNA viruses may overcome mutation-induced defects by several genetic mechanisms. First, error-prone RNA replication can revert mutations (Domingo and Holland, 1997; Drake, 1993). Second, genetic recombination can occur when two distinct viruses co-infect the same cell and exchange genetic information (Kirkegaard and Baltimore, 1986). Recombination can combine mutations on a single viral genome, or "erase" mutations by restoring the viral consensus sequence. Third, fitness may be restored by complementation, whereby two viruses with distinct genetic defects co-infect a cell and these defects are complemented by the functional genome/protein. Fourth, fitness may be

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Conflicts of Interest

The authors declare no conflicts of interest.

restored by reassortment. Reassortment can occur when two distinct, segmented viruses co-infect a cell and generate progeny viruses containing a mixture of segments from both viruses. Genetic mechanisms such as recombination, complementation, and reassortment all require a cell to be co-infected by two, or more, viruses. Overall, these events can promote viral diversity and may enhance pathogenesis of RNA viruses (Dolan et al., 2018; Holmblat et al., 2014; Pfeiffer and Kirkegaard, 2005; Vignuzzi et al., 2006; Xiao et al., 2017).

1.2. Poliovirus as a model to study co-infection

Since its initial discovery in 1909, poliovirus has been extensively studied, initially as a public health threat and later as a model system (Leveque and Semler, 2015; Racaniello, 2006) Poliovirus is a single-stranded non-enveloped RNA virus in the *Picornaviridae* family. As an enteric virus, it is spread through the fecal-oral route. Like other RNA viruses, poliovirus error frequencies during RNA replication are high: approximately one error per replication cycle (Domingo and Holland, 1997; Drake, 1993; Drake et al., 1998; Mansky and Temin, 1995). Indeed, at a high multiplicity of infection (MOI), the poliovirus recombination frequency in cultured cells was 1.3×10^{-3}, meaning that approximately one of every 1,300 genomes is the product of genetic recombination (Kirkegaard and Baltimore, 1986). Recombination of poliovirus has also been observed *in vivo* and there is evidence of poliovirus recombination with other enteroviruses during natural infection in humans (Arita et al., 2005; Cuervo et al., 2001; Dahourou et al., 2002; Furione et al., 1993; Holmblat et al., 2014; Sergiescu et al., 1969; Simmonds and Welch, 2006). Additionally, Holmblat *et al.* found that defective poliovirus genomes were capable of undergoing recombination, thus restoring their fitness *in vivo* (Holmblat et al., 2014). In fact, individuals infected with circulating vaccine derived polioviruses (cVDPVs) are commonly infected with viruses that have undergone genetic exchange (Cherkasova et al., 2002; Cuervo et al., 2001; Dahourou et al., 2002; Furione et al., 1993; Liu et al., 2000). Apart from genetic recombination, complementation of poliovirus genomes has also been observed in infected mice (Vignuzzi et al., 2006). While genetic recombination, complementation, and reassortment of RNA viruses have been observed *in vitro* and *in vivo,* the mechanisms that promote these events have not been fully defined.

2. Aggregation-mediated viral co-infection

Early observations indicated that several viruses can form aggregates, including both enveloped and non-enveloped viruses (Floyd and Sharp, 1977, 1978, 1979; Wallis and Melnick, 1967). For poliovirus, several virions can aggregate in sewage water and viral aggregates may complicate disinfection (Floyd and Sharp, 1979; Young and Sharp, 1977). While aggregation of mammalian viruses has been observed for nearly 50 years, the implication of aggregation as a potential mode of transmission and co-infection had not been studied until recently (Aguilera et al., 2017).

A well-known assumption in virology is that a single infectious unit forms a plaque. This concept is the basis for viral quantification by plaque assay in many viral systems. Intriguingly, recent studies have shown that plaques can be generated by an infectious unit containing more than one virus, thereby creating a “chimeric plaque” (Aguilera et al., 2017;

Combe et al., 2015). We found that, in addition to single viral particles, our poliovirus stocks contained aggregates ranging from 2-10 particles (Aguilera et al., 2017). More importantly, when we induced aggregation by low pH treatment, we observed an increase in the frequency of chimeric plaques (Fig 1 mechanism 1). Interestingly, the frequency of chimeric plaques was increased in viral populations with mutagenized genomes, suggesting that co-infection and subsequent recombination and/or complementation could contribute to productive infection (Aguilera et al., 2017). These results suggest that aggregation can induce viral co-infection and possibly restore viral fitness.

3. Bacteria-mediated viral co-infection

3.1. Intestinal microbiota promote infection of enteric viruses

Mammalian enteric viruses encounter several barriers during infection of the host, including the relatively small number of viruses ingested as well as several physiological and immunological barriers. Therefore, initial infection of the host is likely a low MOI event due to these and other factors. In the last few years, studies from multiple groups have shown that intestinal bacteria play an important role in the infection of several unrelated RNA enteric viruses, including poliovirus, reovirus, rotavirus, mouse mammary tumor virus (MMTV) and noroviruses (Baldridge et al., 2015; Jones et al., 2014; Kane et al., 2011; Kuss et al., 2011; Uchiyama et al., 2014). Bacteria may promote viral infection through direct effects on viral particles or indirect effects on the host (Baldridge et al., 2015; Jones et al., 2014; Kane et al., 2011; Kuss et al., 2011; Li et al., 2015; Pfeiffer and Virgin, 2016; C. M. Robinson et al., 2014; Uchiyama et al., 2014). For poliovirus, the intestinal microbiota was required for efficient replication and pathogenesis in mice (Kuss et al., 2011). More specifically, bacteria increased the attachment of poliovirus to host cells and also limited virion inactivation from heat or bleach treatment *in vitro* (Kuss et al., 2011; C. M. Robinson et al., 2014). Our lab further determined that poliovirus binds to the surface of bacteria, indicating that direct interactions are mediating these effects (Erickson et al., 2018; Kuss et al., 2011; C. M. Robinson et al., 2014). Indirect mechanisms of bacteria-mediated enhancement of enteric viral infection include modulation of the host immune response (Baldridge et al., 2015; Kane et al., 2011). During MMTV infection, virus-bound LPS induced IL-10-mediated immune tolerance (Kane et al., 2011). For murine norovirus, bacteria may dampen IFN-λ mediated effects (Baldridge et al., 2015). Overall, bacteria facilitate infection of several unrelated RNA viruses through several mechanisms.

3.2. Intestinal bacteria promote co-infection of poliovirus

Increasing evidence supports the idea that bacteria promote infection of several mammalian viruses. While it is clear that enteric viruses interact closely with the host microbiota, whether these bacteria influence diversity of these viruses had not been studied until recently. We screened 40 bacterial strains for poliovirus binding and found that nearly all could bind the virus, and multiple virions could bind each bacterial cell (Erickson et al., 2018). Importantly, several of these bacterial strains induced the co-infection of distinct genetically marked polioviruses, even at a low MOI (Fig 1 mechanism 2). Furthermore, co-infection of viruses correlated with the ability of bacteria to adhere to host cells (Erickson et al., 2018). As a result of bacteria-mediated co-infection, genetic recombination occurred

between two distinct parental strains with separate genetic defects, restoring viral fitness of progeny recombinant viruses. Additionally, we determined that bacteria can facilitate the co-infection of multiple distinct parental viruses, with up to 6 different parental viruses observed in a single plaque (Erickson et al., 2018). Overall, these findings indicate that bacteria mediate viral co-infection and may influence viral evolution.

4. Membrane vesicles containing multiple virions can promote co-infection

Several recent studies have shown that co-infection of RNA viruses can occur as a result of non-lytic, cell-to-cell transmission through membrane vesicle structures (Fig 1 mechanism 3). During infection, poliovirus can be packaged in phosphatidylserine-rich vesicles (Chen et al., 2015). This mode of packaging facilitated the transport of several viral particles, and thus co-infection, to neighboring cells *in vitro* (Chen et al., 2015). Importantly, Santiana *et al.* demonstrated that rotavirus and norovirus can be shed in stool within vesicles and that the vesicular form of the virus had enhanced disease severity in mice compared with single particles (Santiana et al., 2018). Additionally, poliovirus and coxsackievirus B3 (CVB3) can exit cells through vesicles derived from autophagosomes, a process referred to as AWOL (autophagosome-mediated exit without lysis) (Bird et al., 2014; S. M. Robinson et al., 2014). Both hepatitis A and C viruses can exit infected cells through exosomes, or vesicle-like structures, thus mediating the transfer of infectious viral particles and RNA to neighboring cells *in vitro* (Dreux et al., 2012; Feng et al., 2013; Longatti et al., 2015; Ramakrishnaiah et al., 2013).

5. Co-infection as a requirement for multipartite viral infection

For certain RNA viruses, such as those with segmented genomes packaged into separate particles, co-infection is a requirement for productive infection. While several mammalian viruses have segmented genomes, the segments of these viruses are packaged into a single viral particle. However, unique to certain plant and fungal viruses, some of these viruses package their genome segments into separate, individual viral particles. Productive infection of these viruses requires these individually packaged particles to infect the same cell simultaneously, a phenomena known as multipartite or multicomponent infection (Ghabrial and Suzuki, 2009; Rao, 2006). Recently, Ladner *et al.* determined that an animal virus has a multipartite genome similar to multipartite genomes of some plant and fungal viruses (Ladner et al., 2016). This enveloped RNA virus, Guaico Culex virus (GCXV), was isolated from *Culex* mosquitoes and is composed of 5 viral segments that are packaged in separate viral particles (Ladner et al., 2016). Interestingly, only 3 viral segments were required for productive infection and subsequent plaque formation (Ladner et al., 2016). While several viral particles are required for efficient infection of some RNA viruses, the mechanisms and consequences of the multicomponent infection process during transmission remain unclear.

6. Conclusions

Increasing evidence supports the idea that viral co-infection is mediated by several mechanisms and potentially at different stages of infection. Cell-to-cell transmission by

virions in vesicle-like structures or aggregates could facilitate the transport of several viral particles and/or genomes from infected cells to neighboring cells. Other factors, such as the presence of bacteria, could also facilitate co-infection during inter-host transmission. These mechanisms of infection also have several implications for viral fitness of otherwise defective genomes. Overall, the studies described here highlight the existence of novel mechanisms that influence co-infection of RNA viruses and potentially promote viral evolution.

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Highlights

- Emerging modes of RNA virus transmission may facilitate viral co-infection
- Viral aggregates can co-infect cells and form chimeric plaques - Bacteria can facilitate viral co-infection and subsequent recombination
- Multiple viruses within membrane vesicles can co-infect cells

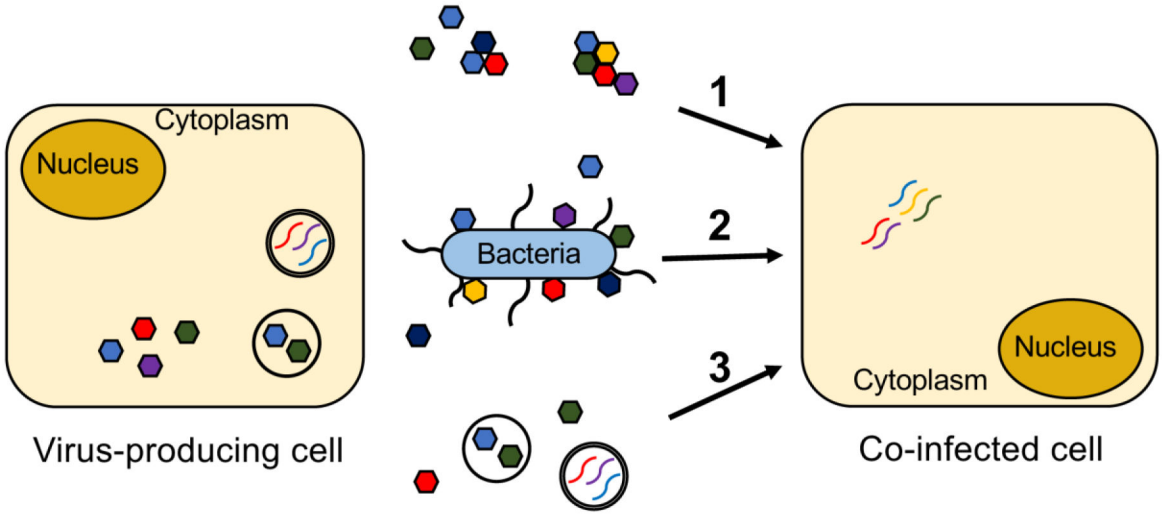

Figure 1.

Mechanisms of viral co-infection. Viral co-infection of mammalian cells can be induced by 1) Virion aggregates, 2) Bacteria bound by several viral particles, and 3) Release of viral particles or viral genomes within membrane vesicles. Genetically distinct viruses are depicted as multi-colored hexagons (virions) or curved lines (genomes).