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The defective component of viral populations

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Particles containing degenerate forms of the viral genome which interfere with virus replication and are non-replicative *per se* are known as defective interfering particles (DIPs). DIPs are likely to be produced upon infection by any virus *in vitro* and in nature. Until recently, roles of these non-viable particles as members of a multi-component viral system have been overlooked. In this review, we cover the most recent studies that shed light on critical roles of DIPs during the course of infection, including: the modulation of virus replication, innate immune responses, disease outcome and virus persistence, as well as the evolution of the viral population. Together, these reports allow us to conceive a more complete picture of the virion population, and highlight the fact that DIPs are not a negligible subset of this population but instead can greatly influence the fate of infection.

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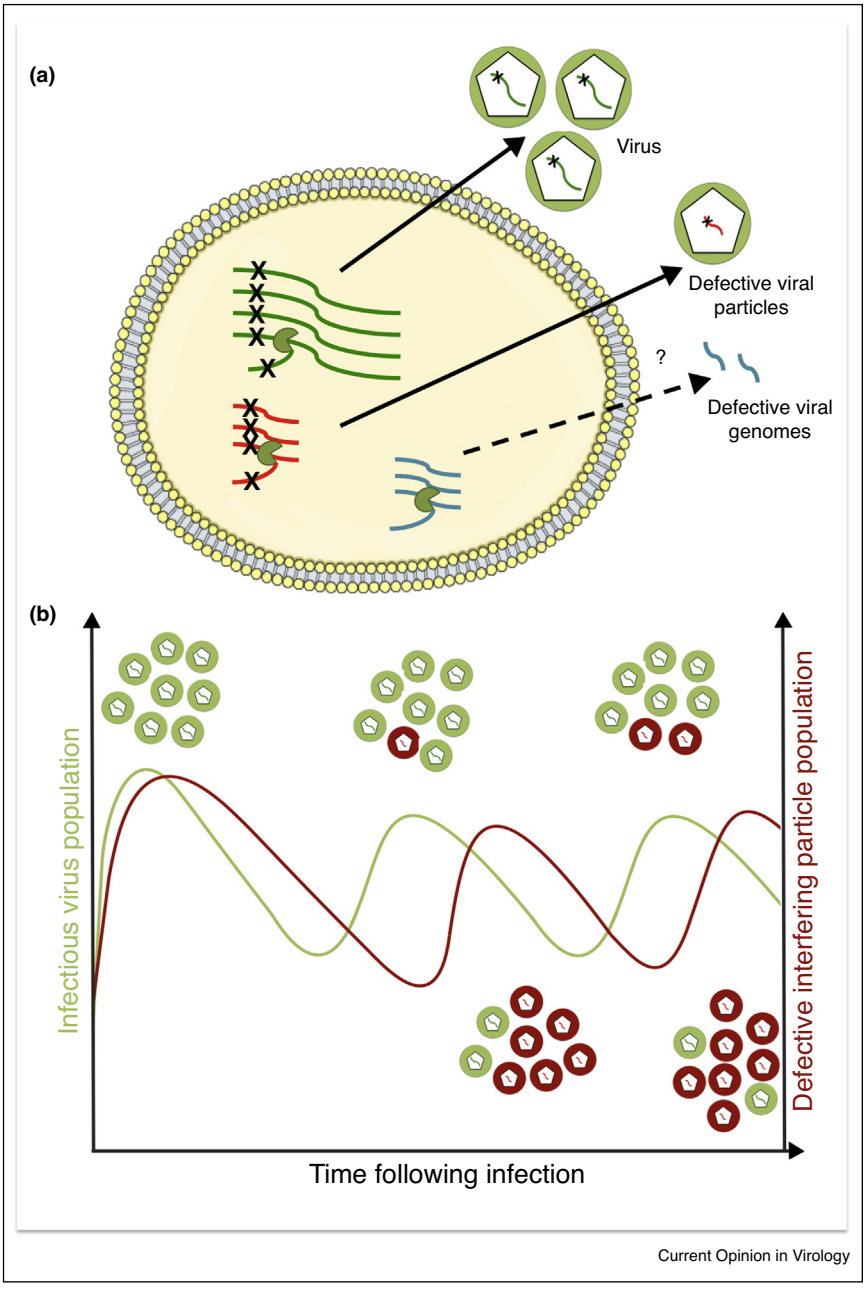
During virus replication at high titer, truncated forms of the viral genome (called defective viral genomes (DGs)) arise. Nonetheless, they can be propagated by complementation with viable wild-type (WT) virus. Besides internal deletions, defective viral genomes can also harbor rearrangements of the genome, complementary ends or simply point mutations that render the RNA non-replicative (or a combination thereof). In addition, those that are amplified and accumulate tend to retain essential signals required for packaging and replication. This review focuses on all sorts of defective interfering particles (DIPs), which interfere with standard virus replication and are different from other non-replicative, non-interfering particles with DGs [1].

DIPs were first described for influenza virus over 70 years ago as a result of successive passages of the virus at high multiplicity of infection (MOI) [2]. Since their discovery, DIPs have been described for nearly every virus family, irrespective of the nature of their genome. Although DIPs were historically considered artefacts of virus propagation *in vitro*, recent reports have shown that defective viral genomes can also be detected in patients infected with influenza A virus [3,4•], dengue virus [5], hepatitis C virus [6,7], respiratory syncytial virus [8•] and birds infected with West Nile virus [9]. DIPs have also been described in plant viruses such as tomato bushy stunt virus, broad bean mottle bromovirus and Turnip crinkle virus [10–12]. The growing number of studies identifying defective viral genomes in clinical and natural isolates suggests that DIPs are not just mere parasites of the viral population, and have sparked interest in elucidating their possible roles. In this review, we consider recent studies that provide evidence of DIPs playing a pivotal role as members of the multi-component viral system: modulating virus replication, influencing disease outcome, triggering immune responses, and promoting virus persistence following infection. Finally, we assess the possible implication of DIPs in shaping virus evolution, an area that remains largely unexplored.

Intracellular interference

In addition to hijacking viral resources, the pool of cellular host factors otherwise utilized for replication by WT virus is also usurped by DIPs. As a consequence, WT virus is out-competed by DIPs, leading to a cyclical pattern between the proportion of DIP and parental virus populations (Figure 1). The current widely held view is that DIP replication is favoured over that of its cognate parental genome due to several factors, including faster replication of the DIP genome because of smaller genome sizes [13]. Small truncations or point mutations in DIPs that do not necessarily have a smaller genome size could also contribute to competition between DI and WT virus RNA replication. For instance, removal of translation enhancer elements in DI RNA results in preference of DIP RNA as a template for replication rather than translation [14,15]. It is also possible that point mutations could enhance DIP RNA replication specifically. In the case of copy-back DIPs derived from negative-strand RNA viruses, a replicative advantage is conferred by the presence of 5′ end elements involved in regulating replication and the lack of 3′ end regulatory elements harboring transcription initiation sites. Although these characteristics may act as contributory factors to intracellular interference with WT virus replication, recent studies hint that the mechanism of DIP hindrance at the intracellular level is much more complex than currently thought. This is best exemplified by recent findings related to a well-known DIP derived from

Figure 1



Schematic representation of defective interfering particles and their generation. **(a)** Replication of the viral genome by the viral polymerase can result in truncated versions of the genome (defective viral genomes), which may be encapsidated and form defective viral particles. **(b)** Schematic representation of periodic fluctuations between defective interfering particles (DIP) and wild-type (WT) infectious virus populations during cultivation of a virus stock in a controlled environment. The representation is inferred from modelling results obtained in [62]. The dependence of DIPs on resources encoded by the infectious virus and its interference effects result in an out-of-phase cyclic pattern between the proportion of DIP and WT virus particles.

influenza A segment 1 (known as 244/PR8). 244/PR8 inhibits influenza A virus (IAV) replication and protects against disease *in vivo* against other non-influenza A respiratory viruses [16]. The mechanism of interference of 244/PR8 with IAV replication was recently demonstrated to occur through competition for packaging with segment 1 of the WT virus and replacement of this segment in the majority of progeny virions [17]. This same DIP inhibited transcription from the parental and other segments, but intriguingly not all segments, illustrating the complexity and our poor understanding of DIP interference at the molecular level. Possibly, not one but