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Current Opinion in Virology

Virus population dynamics during infection

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During RNA virus infection of a host, error-prone viral replication will give rise to a cloud of genetically-linked mutants, as well as truncated, defective genomes. In this review, we describe the dynamics of viral diversity during infection, illustrating that the viral population fluctuates greatly in number of genomes and composition of mutants, in relation with the existence of physical barriers or immune pressures. We illustrate the importance of generating diversity by analyzing the case of fidelity variants, largely attenuated *in vivo*. Recombination is also considered in its various roles: redistribution of mutations on full-length genomes, and production of highly-immunostimulatory defective genomes. We cover these notions by underlining, when they exist, the differences between acute and persistent infections.

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Current Opinion in Virology 2017, **23**:82–87

This review comes from a themed issue on **Viral pathogenesis**

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Edited by **Raul Andino** and **Michael Diamond**

For a complete overview see the Issue and the Editorial

Available online 26th April 2017

http://dx.doi.org/10.1016/j.coviro.2017.03.013

Introduction

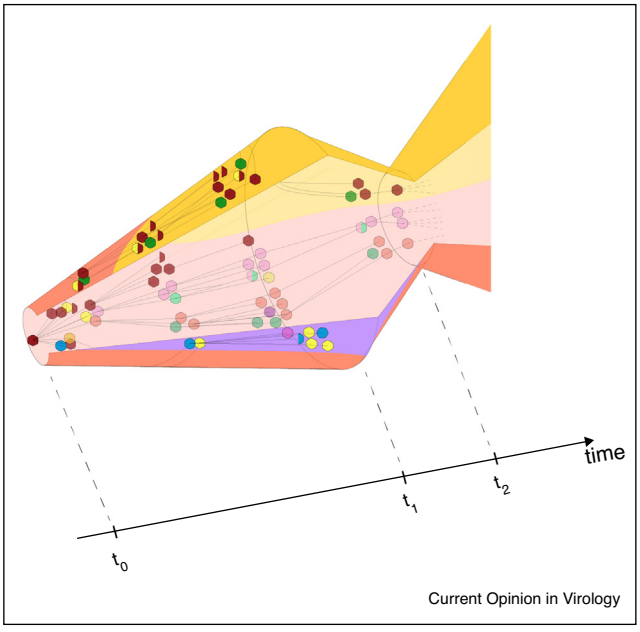
RNA virus populations are highly dynamic, due to short generation times, large population sizes, and high mutation frequencies. A number of parameters intrinsic to the replication cycle and its machinery affect these dynamics. Replication is ensured by an error-prone viral RNA-dependent RNA polymerase, with mutation rates ranging from 10^{-6} to 10^{-4} mutations/nucleotide/infection cycle [1]. Consequently, a heterogeneous population of closely related mutants is produced during infection, referred to as a mutant spectrum or quasispecies [2]. Additionally, viral diversity can be altered by copy-choice recombination, when the viral polymerase switches templates during replication. Furthermore, segmented viruses, such as Influenza A viruses, undergo reassortment of genetic segments during coinfection.

In this review, we describe the dynamics of RNA virus diversity during infection, and assess the implications of viral population dynamics in pathogenesis and transmission. We delineate the role of host pressure, mainly arising from immune systems, in shaping viral diversity. We rely mostly on data generated in HIV and HCV-infected patients. Studies on Influenza viruses help analyze the role of reassortment, while arboviruses, such as dengue virus or chikungunya virus, will be considered punctually in terms of host switching and transmission. Overall, despite a wide variety of infection strategies, depending on the virus and the colonized host, important features can be delineated governing the population dynamics of viral infection.

Bottlenecks and fluctuations in population size during infection

Infection involves the colonization of different host compartments, during which considerable fluctuations in viral diversity can occur in a spatial and temporal manner. Viral population size changes during infection, and even when titers remain constant, the population is turning over. While fast replication gives rise to numerous progeny, viral populations undergo severe loss in size when host barriers or selective pressures are encountered. Such bottlenecks trigger an important reduction in virion number that can have consequences on viral diversity (Figure 1, between t_1 and t_2). Population bottlenecks are frequently observed at the initial site of infection: for example, dengue virus faces a major bottleneck while crossing the mosquito midgut, with as little as 5–42 founder viruses crossing this anatomical barrier to initiate infection [3•]. HCV and HIV infection are believed to start with a single or few particles [4,5,6••]. The transmission stage can also constitute a strong bottleneck: for influenza A virus, a small number of variants (two to five in guinea pigs) are transmitted, depending both on the infected species and the mode of transmission (aerosol being more stringent than contact transmission) [7••]. Moreover, intra-host bottlenecks may exist at other anatomical barriers. For dengue and chikungunya viruses, an additional bottleneck occurs at the salivary gland in mosquitoes [8,9]. Overall, bottlenecks and other selective pressures will trigger fluctuations in the number of virions present during infection. Concomitantly, the variation in the total number of virion impacts the multiplicity of infection (MOI), or the number of viruses that can infect an individual cell [10]. Thus, the MOI also fluctuates during infection: in turnips infected with Turnip Mosaic virus, companion cells are infected at a MOI of 0.07 during the initial infection, but secondary infections of the mesophyll have MOI ranging from 21 to 41 [11•].

Figure 1



Schematic of viral dynamics during intra-host evolution.
The diagram represents the dynamics of viral diversity over time (bottom axis). Diameter of the cone at a given time relates to the overall size of the population. Initial infection at t_0 by a single virion (depicted as a red dot) is followed by an expansion of the population until t_1. A bottleneck arises between t_1 and t_2, and the population's size shrinks, before expanding again. Each color at the surface of the cone stands for a particular compartment of the host. Each colored dot represents a particular viral genotype. Progeny is linked to parental virus by lines, as in a phylogenetic tree. Recombinant progeny is depicted as bicolor, and defective genomes are represented as half dots.

Importantly, MOI greatly influences the size of the bottleneck, as well as genetic exchanges within the viral population, allowing processes such as recombination and reassortment upon coinfection.

Fluctuations in viral diversity during infection

In addition to changes in population size, viral populations fluctuate both spatially and temporarily in their genetic composition (Figure 1). During HIV infection, viral subpopulations are spatially segregated, evolving independently in the brain and blood of patients [12–14]. Viral evolution is thus not necessarily homogeneous throughout the organism, but rather responds to organ or even cell-type specialization. Moreover, evolution of the population over time is a well documented process, particularly in HIV and HCV-infected patients, both of which are persistent infections. HCV evolved rapidly in infected patients, with the establishment of different lineages within the same host, suggesting compartmentalization of viral replication for long periods of time [5,15••]. In HIV-infected patients, it was suggested that viral populations also display continuous evolution, but without the establishment of distinct lineages [6••,16]. Finally, the type of HIV minority variants accumulating through time is reproducible between patients not treated with antiviral drugs, implying that forces driving selection are common between different individuals [6••]. In the course of HIV or HCV persistent infections, consensus sequences can change due to accumulated mutations linked to variant selection and/or genetic drift. This is less likely during acute infection, due to shorter periods of active viral replication, even if physiological barriers such as bottlenecks can greatly influence the quasispecies composition and promote the stochastic selection of a variant to take over the population.

Mutation in population dynamics

The introduction of mutations in the viral genome during replication by the error-prone polymerase is a key driver of viral diversity. As such, viral populations arising during host infection constitute a cloud of genetically-linked mutants, rather than a homogeneous population. In addition to the polymerase and its mutation rate of approximately 10^{-4} mutation/nucleotide/infection, cellular factors can play a role in mutating viral genomes [1]. HIV, for example, is also subjected to the error rate of the RNA polymerase II, when HIV DNA is transcribed, as well as to the mutagenic activity of the restriction factor APOBEC3G [17,18]. To assess the role of the quasispecies in viral pathogenesis, numerous studies have used fidelity variants. These viruses, point mutated in a protein of the viral replication complex, have either a higher mutation rate (mutator) or a lower mutation rate (high fidelity variant) compared to the wildtype virus [19,20•]. It was first demonstrated that a high-fidelity variant of poliovirus was impaired in its ability to invade the central nervous system [19]. Treating with the mutagenic compound ribavirin in order to generate a wildtype-like population rescued the virus' neurotropism. Since then, numerous fidelity variants have been identified in various viral families [21]. Interestingly, the vast majority of these variants, despite showing a wildtype-like phenotype in cell culture, are attenuated *in vivo*, apart from a high-fidelity mutant of foot and mouth disease virus [22]. H5N1 high-fidelity variant showed a strong attenuation in mice, as well as mutators of chikungunya virus and Sindbis virus which were attenuated both in mice and insect models [20•,23]. To conclude, viral diversity generated during viral replication seems pivotal to the success of an infection, as viruses that deviate from wildtype mutation rates show strong attenuation *in vivo*, and are not generally observed in nature.

Recombination in population dynamics

Copy-choice recombination – a general feature of RNA viruses – allows the generation of viral genomes bearing unique combinations of mutations through template-switching during polymerization (Figure 1) [24]. In an attempt to assess the role of recombination in poliovirus