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Current Opinion in Virology

How does the genome structure and lifestyle of a virus affect its population variation?

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Viruses use diverse strategies for their replication, related in part to the genome structure (double-stranded or single-stranded; positive sense or negative sense; RNA or DNA). During each round of replication, mutations are introduced in the viral genome and the mode of replication (stamping machine and geometric replication) may affect the population dynamics of the progeny virus. Our understanding of the relationships among genome strandedness, mode of replication and the population variation is still limited. Here we will review what is known about virus replication by stamping machine or geometric modes, and how that relates to the biology of single stranded versus double stranded RNA genomes. We will present how this may affect the mutation frequency and population dynamics. Finally the potential importance of the population dynamics in acute viruses and persistent viruses will be discussed.

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Current Opinion in Virology 2014, **9**:39–44

This review comes from a themed issue on **Virus replication in animals and plants**

Edited by **C Cheng Kao** and **Olve B Peersen**

For a complete overview see the Issue and the Editorial

Available online 20th September 2014

http://dx.doi.org/10.1016/j.coviro.2014.09.004

Introduction

Error-prone replication, large population sizes, and rapid replication lead to large clouds of mutants in RNA viruses [1], and RNA viruses are often characterized by high levels of genetic variation known as quasispecies. The quasispecies nature of viruses leads to many biological consequences. Having a large mutant cloud size provides an accessible pool of mutants that could benefit the virus during adaptation to a new environment or escape from the host defenses, sometimes resulting in emerging viral diseases [2]. Conversely, highly diverse populations subjected to repeated bottlenecks can lose fitness through a process known as Muller's ratchet [3], as demonstrated in a number of studies with *Vesicular stomatitis virus* [4–7].

The viral RNA dependent RNA polymerases (RdRps) are thought to have low fidelity due to a lack of proofreading [8]. DNA dependent DNA polymerases require basepairing of a primer to initiate polymerization, but this is not required for transcription initiation in RNA polymerases, and RNA viruses may be more relaxed in this level of fidelity as well [9]. Although the replicase fidelity determines the mutation rate of viruses, their genetic variation also is governed by natural selection and genetic bottlenecks. Here we use 'mutation rate' to refer to how often the polymerase makes a mistake, while 'mutation frequency' refers to the accumulation of mutations after (unknown) rounds of replication, bottlenecks and selective events [9]. Schneider and Roossinck [10] showed that mutation frequency is host associated, and the population variation of *Cucumber mosaic virus* (CMV) in pepper is higher than that in tobacco. Additional studies show the role of host factors in virus replication [11,12]. The impact of translation elongation factors in RNA virus replication was reported first in bacteriophage Qβ by Blumenthal *et al.* [13]. Later, the effect of the translation elongation factor 1A (eEF1A) in the synthesis of *Tombusvirus* negative strand was demonstrated [11].

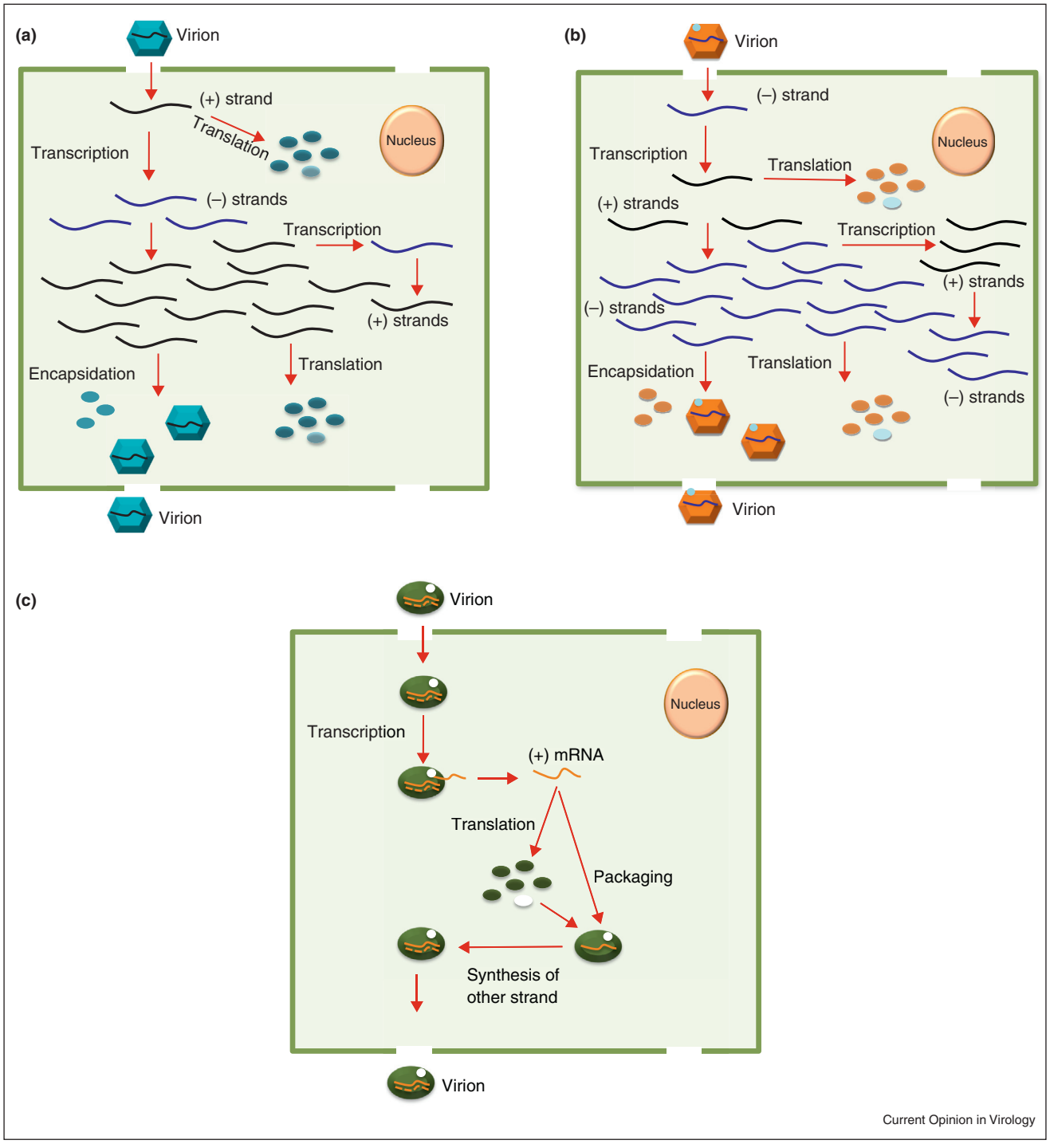
Some single stranded (ss) DNA viruses, which use a host polymerase, have similar levels of mutation frequency as RNA viruses [14,15]. Thus, the difference between RNA and DNA virus population variation does not necessarily reflect what is known about the polymerase fidelity. Beside the error rate of viral polymerase, there are other factors affecting the frequency of mutant viruses during an infectious process, including the amplification dynamics of RNA positive and negative strands and purifying mechanisms acting after the transcription. Here, we focus on the dynamics of different RNA strands. We will briefly explain the replication cycle in RNA viruses with different genome structures and their mode of replication, and discuss how the dynamics of positive and negative strand RNA can affect the mutation frequency, and how all these factor are related to the lifestyle of viruses.

Replication cycle in RNA viruses

Viral genomes are either RNA or DNA, which can be double stranded (ds) or single stranded (ss). Based on the polarity of their genomic RNA, ssRNA viruses are classified into positive (+) and negative (−) sense viruses.

In (+) ssRNA virus, once the virus enters the cytoplasm of an infected host cell, it is uncoated (Figure 1a), and then becomes immediately available for translation as an

Figure 1



Life strategies for RNA viruses with different genome types **(a)** (+) ssRNA virus life cycle. **(b)** (–) ssRNA virus life cycle. **(c)** Life cycle for dsRNA viruses.

mRNA. During translation the structural and non-structural proteins, including RdRp and other required proteins for virus replication, are produced. The third step is transcription; the (–) strands (antigenomic strands) are copied from the genomic strand. These (–) strands are used as templates for (+) RNA synthesis as progeny genomes or amplified mRNAs. The replication process in (+) ssRNA viruses is usually asymmetric, and a large excess of positive over negative strands is produced [16–19]. Finally, in most cases genomes are