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Evidence for Quasi Species in Severe Acute Respiratory Syndrome–Associated Coronavirus Deletion Mutants

Using specimens obtained during the 2003 epidemic in Hong Kong, Tang et al. have reported data on a 386-nt deletion in severe acute respiratory syndrome–associated coronavirus (SARS-CoV) [1]. Because 1 patient had both the L386del variant and the wild-type variant in the same specimen, they raised the possibility that SARS-CoV exists as a quasi species, at least in some patients. Previous authors studying single-nucleotide variants from Beijing-area isolates in 2003 [2] and from the Singapore 2004 outbreak [3] have also found multiple viral sequences in the same sample that they attributed to quasi species. Although these 3 studies clearly establish the presence of a diversity of SARS-CoV genomes in individual patients, the issue of whether SARS-CoV quasi species exists remains open, particularly with respect to the 386-nt deletion.

The concept of quasi species was described by Eigen et al. to indicate a "complex, self-perpetuating population of diverse related entities that act as a whole" [4, p. 42; for review, see 5]. The earliest experimental verification of the theory was obtained with the bacteriophage Qβ, in which the wild type existed only as the weighted average of different sequences [6]. Eigen has acknowledged, however, that in instances in which the characteristics of a heterogeneous population had not been established, it might be more appropriate to call the population a "swarm" rather than a quasi species [7]. This distinction could be particularly pertinent to the large deletion described by Tan et al., because the resulting swarm lacks a prominent mechanism for the maintenance of quasi species, the ability to back-mutate point mutations.

The finding of the L386del variant along with the intact genome has at least 3 possible implications. The first is the issue of whether the gene products of the deleted segment are either virulence factors or essential for viral replication. The 386-nt deletion disrupts open reading frame (ORF) 9 and eliminates ORF 10 and 11. The functions of the products of these 3 ORFs are currently unknown. However, they could be essential and involved with virulence, the functionality being supplied by other genomes in the swarm. The second is the possibility that the deletion variants produce truncated protein that acts as a decoy for the immune system [8]. Last, although the deletions are usually much larger, the deletion mutant could be an early stage in the development of defective interfering particles.

Because of safety considerations, additional experiments involving growth and separation of viruses with the different genomes may not be advisable. However, if sufficient patient material is available, multiple clones could be obtained from polymerase chain reaction products and the percentage of genomes with the deletion determined for various stages of both infection in the individual patient and the course of the epidemic. The finding of patients with severe disease who did not have full-length variants would support the idea that the deletion mutants were both fully infectious and virulent. On the other hand, as is consistent with the data in figure 2 of the Tang et al. article [1], the finding of progressive increase in the percentage of genomes with the deletion mutants would support the hypothesis of defective interfering particles.

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