25e Population Dynamics of Defective Interfering Virus-like Particles

Kristen Stauffer and John Yin

Defective interfering (DI) particles are virus-like particles that are formed as a byproduct of natural and laboratory viral infections. The propensity to generate and propagate DIs is a common feature of many viruses, including bacteriophage, influenza virus, poliovirus, and vesicular stomatitis virus (VSV). DIs typically carry large deletions in essential functions, making their replication dependent on complementation by co-infecting standard virus. Moreover, they interfere with the replication of standard virus by acting as a parasite to the infection, competing for limited replication resources. Interactions between DI and standard virus particles during an infection may have vastly different outcomes. DIs can mitigate an infection or increase its pathogenesis. The effects of an infection may be reduced when DIs simultaneously depress standard particle yields and activate innate and adaptive immune responses.[1, 2] DIs can also aid in establishing a persistent infection, which can lead to further complications, such as encephalitis, and possibly death.[3]

It is well accepted that DIs arise most readily under conditions of high multiplicity of infection (MOI) passage, where many virus particles infect a single cell. However, it is not known what MOIs are necessary or sufficient for DI formation and propagation. We have performed controlled passaging of VSV on baby hamster kidney (BHK) cells at MOIs of 100 to 10^{-4}. We have found that the virus yield drops by two orders of magnitude (from ~10^9 to ~10^7 plaque forming units/ml) in four passages for a controlled MOI of 100 and in five passages for a controlled MOI of 10. For the lower MOIs, the yield has not been as significantly affected.

To better understand the dynamics of DI and standard virus particles we have extended a model developed by Kirkwood and Bangham.[4] The original model is able to predict the general behavior of DIs and standard virus particles. However, the parameters used do not fit the kinetics of growth of VSV grown on BHK cells, nor does it account for controlled MOI passaging. We have adjusted the model to account for the kinetics of this particular experimental system and have added the ability to passage at controlled MOIs. The extended model now accounts for the growth rate of the virus under various MOIs. In addition, the model is able to capture the yield reduction of the standard virus over multiple passages at various MOIs. This study has implications for understanding the pathogenesis of viral disease, developing robust anti-viral therapies, and impacting applications of viruses in oncolytic and gene therapies.

References

1. Holland, J. J. 1990. Defective Viral Genomes, p. 151-165. In B. N. Fields, D. M. Knipe, et. al. (ed.), Virology. Raven Press, Ltd., New York.

2. Sekellick, M. J. and P. I. Marcus. 1982. Interferon induction by viruses. VIII. Vesicular stomatitis virus: [+/-]DI-011 particles induce interferon in the absence of standard virions. Virology 117:280-285.

3. Holland, J. J. and L. P. Villarreal. 1974. Persistent noncytocidal vesicular stomatitis virus infections mediated by defective T particles that suppress virion transcriptase. Proc. Natl. Acad. Sci. U. S. A. 71:2956-2960.

4. Kirkwood, T. B. and C. R. Bangham. 1994. Cycles, chaos, and evolution in virus cultures: a model of defective interfering particles. Proc. Natl. Acad. Sci. U. S. A. 91:8685-8689.