Virus population dynamics and evolution

Viruses undergo a numerous replication cycles as they are transmitted from host to host. During this process spontaneous mutants are continually generated, some of which have biological properties that are different from the parental virus. Some of these mutants can be selected by environmental pressures and by the preferential ability of particular viruses to be transmitted. Properties that play an important role in the survival of viruses include: (i) capacity to replicate rapidly and to reach high titers; (ii) capacity to replicate in certain tissues and to be shed for long periods of time; (iii) capacity to elude host defense and survive external environmental conditions. The emergence of a viral disease often reflects evolutionary change in the causal agent. Many viruses, in particular RNA viruses, have fairly high mutation rates and short generation times. As a consequence of the elevated mutation rate combined with natural selection, many viruses can rapidly adapt to changes in their environment. Virus evolution is an important aspect of the epidemiology of viral diseases and also is a important factor for the success, or lack thereof, of antiviral drugs, as resistance mutations often appear within weeks to months after the beginning of the treatment.

While a handful of effective antiviral therapies have been developed, many of them are tempered by the emergence of resistant variants. On the other hand, viral vaccine development is one of the great successes of modern biomedical research. Different types of vaccines have been developed: attenuated live virus vaccines, inactivated virus vaccines, and subunit vaccines. Attenuated live virus vaccines are the most effective and successful types. However, one problem associated with this type of vaccine is that reversion back to pathogenic forms. Understanding the mechanism of virus evolution is essential to both development of antiviral therapies and vaccine design.

In contrast to classic genetic concepts suggesting that evolution occurs through the selection of individual viruses, the quasispecies theory proposed, based on theoretical considerations, that evolution occurs through selection of interdependent viral subpopulations. We recently isolated and employed a "high fidelity" poliovirus mutant to demonstrate that the diversity of the quasispecies per se is a critical determinant of pathogenesis.

Our results indicate that there is interplay between different variants in the quasispecies so that one mutant allows other mutants to enter the brain. Thus, complexity of the viral quasispecies enables the virus population to spread systemically and successfully access the central nervous system, perhaps by the complementing functions of different subpopulations that facilitate adaptation to new environments. These results put the issue of pathogenesis into almost an ecological perspective. Thus, certain variants within the population may facilitate the colonization of the gut, while another set of mutants may serve as immunological decoys that trick the immune system and yet another subpopulation may facilitate crossing the blood-brain barrier.

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