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Neurovirulence and the genetic structure of the virus quasispecies

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An RNA virus population does not consist of a single genotype; rather, it is an ensemble of related sequences, termed quasispecies. High mutation rates of RNA viral replication create a 'cloud' of potentially beneficial mutations at the population level, which afford the viral quasispecies a greater probability to evolve and adapt to new environments and challenges during infection. Using poliovirus as our model we developed strategies to increase or reduce the mutation rate of the viral polymerase thus changing the levels of genomic diversity in the viral population. In infected animals, reducing or increasing viral diversity leads to loss of neurotropism, and an attenuated pathogenic phenotype. These findings suggest that quasispecies diversity is finely tuned to ensure evolutionary survival of the virus and is a biological determinant for the outcome of poliovirus infection. Our study uncovered a surprising property of the virus population, in which different variants within the quasispecies experiment a cooperative interaction so that some variants allow others to enter the brain. Furthermore, while the viral population with restricted genomic diversity replicate robustly in small intestine, we were unable to isolate viruses from feces of infected mice. This observation suggests that quasispecies diversity plays an important role in virus spread from individual to individual. Interestingly, Sabin vaccine strains are restricted quasispecies, suggesting that population diversity is, at least in part, the basis of attenuation in poliovirus vaccine strains. Thus, altering the structure of the quasispecies result in attenuation of the virus and may provide a novel, rational and general approach for the development of safe live-attenuated virus vaccines.