the Sabin 3 IRES led to the virus' CNS-specific attenuation. Similarly, tissue-specific expression and differential RNA-binding properties of PTB and nPTB are important determinants of neurovirulence of the GDVII strain of Theiler's murine encephalomyelitis virus (97).

ROLE OF QUASISPECIES IN PV PATHOGENESIS

The quasispecies of PV plays an important role in PV pathogenesis (see Chapter 12). PV, as well as other RNA viruses, has a high error rate in RNA replication, and therefore each viral genome in the population differs from others by one or more mutations. In the presence of selective pressures, the quasispecies is presumed to provide an advantage to survival of the viral population as a whole, since some of the mutants contained in the population may be able to adapt to new environments (17, 18). Interestingly, a single point mutation in the RNA-dependent RNA polymerase (3D-G64S) determines the polymerase fidelity, and virus containing this mutation exhibits a reduced error rate (93) (see Chapter 13). The 3D-G64S mutant and wt virus showed few differences in growth kinetics in cultured cells that were not under selective pressure; however, when wt and mutant viruses were propagated in the presence of guanidine hydrochloride, the frequency of appearance of guanidine-resistant virus in the presence of guanidine hydrochloride was lower in the mutant virus (111). This result suggested that the fitness to a new environment was decreased as a result of the high fidelity of the polymerase. Surprisingly, the 3D-G64S virus showed reduced neurovirulence when inoculated by a peripheral route into PVR tg mice but was able to replicate in the CNS when inoculated directly into the CNS (95, 111). These results suggested that a diversity of the PV genome is necessary for adapting to different external conditions during virus dissemination into different parts of the body. A virus population with diverse genomes is likely to contain an individual viral genome that could be a source of a founder that fits well in new environments, while candidate viruses are not likely to be present in a homogeneous population. Pfeiffer and Kirkegaard (94) infected a mixture of tagged PV from the peripheral routes and showed that only a subset of members of the infected pool of virus reached the CNS, suggesting that only a small number of viruses survived and were selected in certain situations. This bottleneck effect was not observed when tagged PV was inoculated in the peripheral sites of PVR tg mice deficient in the type I IFN response (59), suggesting that the quasispecies is required during the dissemination of PV in order to evade the IFN response by the host. Additional studies are needed to elucidate the importance of quasispecies in the pathogenesis of poliomyelitis (see Chapter 12).

CONCLUDING REMARKS

We have summarized barriers against PV infection in the host and mechanisms by which PV passes through them. In the late 1980s, two important findings were made: identification of the PVR, with the subsequent development of PVR tg mice, and identification of the IRES. As a result of these two breakthroughs, investigations of the pathogenesis of PV infection in the whole organism made significant progress; however, many features related to the pathogenesis of PV-induced disease remain unknown. In order to better answer some of the many unsolved questions, knowledge of additional new mechanisms and concepts important in PV infection may be required.

There are several topics that remain poorly understood and could provide important additions to our understanding of PV pathogenesis. (i) The mechanisms by which PV invades two physical barriers, the GI tract and BBB, need to be elucidated, because it is difficult to explain this invasion simply on the basis of PVR-dependent infection. It may be that invasion of these barriers is mediated by transcytosis and that identification of a receptor for transcytosis, rather than the PVR (receptor for infection), mediates PV entry into the GI tract and BBB. (ii) It is not known why the IFN response occurs in a tissue-specific manner upon PV infection and why extraneural tissues are protected by this response while neural tissues are not. It may be that the IFN response varies because of the sensing mechanism for viral replication. Therefore, studies on the viral sensors and molecules that execute the IFN response following PV infection may answer these questions. (iii) It is not known why PV preferentially infects motor neurons in the spinal cord. It may be that an additional factor(s) that is present in other areas of the CNS inhibits PV infection. (iv) PV uses PVR when it reaches the parenchyma of the CNS by means of axonal transport. Although the structural transition of the PV virion is initiated by binding the PVR, uncoating of the virion does not occur during axonal transport but begins in the soma of the neurons. It is possible that the number of PVRs that bind the virion may determine the fate of the PV particle, i.e., a small number of PVRs that bind each virion may not be sufficient to result in viral conformational change but may be able to induce endocytosis of the virus on the surface of synapses. Alternatively, a cellular factor(s) that inhibits viral uncoating could exist in the axon. If this were the case, the virus would need to be free from such a factor(s) before replicating in the neural cell body. (v) The role of the quasispecies in PV dissemination remains unclear and needs to be explored.

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