INTRODUCTION

JC virus is a human papovavirus that has been implicated as the causative agent in the chronic human demyelinating disease progressive multifocal leukoencephalopathy (PML). Although the virus is widespread in human populations, PML in a rare opportunistic disease that occurs primarily in patients with compromised immune systems. The incidence of PML has increased recently in association with HIV infection. Numerous studies have shown viral particles within abnormal oligodendrocytes from PML brains and the aetiology of demyelination is thought to be due to lytic destruction of these myelin-forming cells. Astrocytes can have bizarre morphologies in PML brains that include some features of transformed cells. Virions are rarely found in electron micrographs of these morphologically altered cells.

When inoculated into newborn hamsters JC virus causes a variety of tumours derived primarily from neural tissue. JC virus is the only human virus known to cause tumours in primates (owl and squirrel monkeys) where grade IV astrocytomas or glioblastomas develop 18–24 months after intracranial injection. JC virus has not been shown to induce any detectable pathology when injected into mice. Therefore experimental models addressing the possible mechanism of JC virus-induced demyelination have not been available.

To bypass host range restrictions and to obtain JC virus sequences in every cell of the mouse, transgenic mice have been produced by introducing the early region of the JC virus genome into fertilized mouse ova. The purpose of the present chapter is to describe morphological alterations that occur in strains of JCV transgenic mice. In addition, the molecular basis for demyelination in the most severely affected strain (JC-48) of JCV transgenic mice is reviewed and the role that JC virus T-antigen expression may have in the pathogenesis of dysmyelination is discussed.
VIRUS INFECTIONS AND THE DEVELOPING NERVOUS SYSTEM

TRANSGENIC MICE

JC virus early region DNA was micro-injected into pronuclei of fertilized mouse eggs as described by Gordon and Ruddle\textsuperscript{12}. The early region of JC virus contains the origin of replication, the transcriptional control region and the genes encoding large and small T-antigens. Structural viral proteins are encoded in the late region and were not included on the constructs injected. Therefore, no productive viral infection can occur. T-antigens, the only JC viral proteins that can be expressed in these mice, are pleiotropic transforming proteins found in both the nucleus and cytoplasm of papovavirus transformed cells\textsuperscript{10}. T-antigens appear to play a role in regulating DNA replication and gene expression and are also thought to have a number of functions within the cytoplasm\textsuperscript{10}.

Ten animals containing complete copies of JCV early region DNA were identified\textsuperscript{11,13}. Five of these mice were born dead or died shortly after birth. No analyses were performed on these mice. The other five animals survived varying lengths of time and expressed JCV T-antigens. Three females developed adrenal medullary neuroblastomas and died at approximately 14 weeks of age. Two males survived up to 10 months of age and are the basis of the lines established. One line (strain 48) is derived from a mosaic founder mouse (incorporation of JCV DNA occurred after the pronuclei stage) in which 20\% of the offspring contain intact JC virus early region DNA in all cells. The other line (strain 91) is derived from a non-mosaic JC founder in which 50\% of the offspring contain intact JC virus early region DNA in all cells.

BEHAVIOURAL PHENOTYPE

The offspring of JC-48 appeared normal at birth. However, at 2 weeks of age approximately 20\% of the animals developed a severe tremor that was readily apparent when the mice were moving, but not when they were at rest. Analysis of tail DNA for JC virus early region by the Southern blot technique revealed that only the mice which displayed the neurological phenotype contained intact copies of JC virus early region\textsuperscript{11}. The affected JC-48 mice began to exhibit tonic seizures at 3 weeks of age, most died by 4 weeks and none lived past 6 weeks of age. Since no affected mice lived to maturity, a permanent line of JC-48 mice was not established.

Approximately 50\% of the offspring of JC-91 exhibited a similar but less severe neurological phenotype. A slight tremor became evident 3–4 weeks after birth. Only those JC-91 mice displaying the neurological phenotype contained intact copies of JC virus early region. Affected JC-91 mice were healthier than JC-48 mice and lived to 2–5 months of age. JC-91 mice have been successfully bred and homozygous offspring identified. The severity of the neurological dysfunction in JC-91 homozygotes is intermediate to that found in JC-48 and JC-91 heterozygotes. JC-91 homozygotes express a shaking phenotype at 2 weeks of age and none live past 4 months of age.