

Viral determinants of JCV tropism



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JC virus is a common human polyomavirus that infects over 70% of the population worldwide. In immunosuppressed individuals, JCV causes a lytic infection of oligodendrocytes, resulting in the fatal, demyelinating disease PML. JCV has a cell tropism that is restricted to oligodendrocytes, astrocytes and B lymphocytes. Both viral and cellular factors have critical roles in determining host cell susceptibility. We are interested in characterizing the viral determinants of tropism, specifically, the role of the viral capsid structure in the JCV lifecycle. Although VP1, the major capsid protein of JCV, has not been co-crystallized with the cellular receptor, we have created a molecular model based on previously determined capsid structures of other closely related polyomaviruses. This model has enabled us to identify amino acids that are potentially important in virus-receptor interactions and has allowed us to create a series of mutant JC viruses with amino acid substitutions in the VP1 sequence. Characterization of these mutants through examination of virion viability, stability and infectivity has allowed us to identify specific residues that are critical determinants of JCV tropism and may define the receptor binding pocket.