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Guest Editorial

Genotypes, archetypes, and tandem repeats in the molecular epidemiology and pathogenesis of JC virus induced disease

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The human polyomavirus JCV is ubiquitous, infecting greater than 70% of the population worldwide, (Berger and Major, 1999; Hou and Major, 2000). Once infected with JCV the virus is harbored for life with generally no adverse consequences. In a minority of immunosuppressed patients the virus gains access to the CNS and targets both oligodendrocytes and astrocytes. Lytic viral replication in oligodendrocytes results in a rapidly progressing and uniformly fatal demeyelinating disease known as Progressive Multifocal Leukoencephalopathy (PML). Approximately 4–5% of AIDS patients develop PML and the majority succumb to the disease within one to two years of diagnosis. To date there is no specific therapy that has been successful in the treatment of PML.

There are several major unresolved issues regarding the interactions of JCV with its host under both normal and immunosuppressed conditions. First, the mode of virus transmission is not completely understood but almost certainly involves direct human-to-human transmission by a fecal oral route. The fecal oral route of transmission is suggested by the fact that virus is excreted in the urine and is a common contaminant in untreated urban sewage (Bofill-Mas *et al*, 2000, 2001). Virus has also been frequently detected in tonsillar tissue suggesting that transmission may also occur by a respiratory route (Lisignoli *et al*, 1997; Monaco *et al*, 1996, 1998). It should be noted here that poliovirus was once frequently detected in human tonsil despite clear evidence for fecal oral transmission of this virus. Second, the sites of viral persistence have not been unequivocally identified. The kidney is one site of obvious viral persistence as virus is frequently shed in the urine (Arthur *et al*, 1989; Bofill-Mas *et al*, 2000, 2001; Shah *et al*, 1997). Virus has also been frequently detected in a number of lymphoid tissues including lymph node, spleen, and bone marrow suggesting that lymphoid organs represent a major site of virus persistence (Houff *et al*, 1988; Koralnik *et al*, 1999; Monaco *et al*, 1998; Schneider and Dorries, 1993; Tornatore *et al*, 1992). Within these lymphoid organs virus is often found associated with B cells and B cells have been shown to support low levels of virus growth (Monaco *et al*, 1996). In one study JCV infected B cells were detected in PML brain, which strongly supports the hypothesis that B cells may traffic JCV into the CNS to initiate disease (Major *et al*, 1990). Third, and perhaps most pressing is the question of why only 4–5% if patients develop PML when clearly the majority of these patients are already infected with virus. This has led to a fairly exhaustive search for genotype specific differences in JCV that may correlate with the development of PML. JCV genomes isolated and sequenced directly from human tissues have been found to have a highly variable noncoding regulatory region, most often referred to as the transcriptional control region (TCR), and a well conserved coding region. Silent mutations within the highly conserved coding region of the major capsid protein VP1 have been used to divide JCV genomes into eight types (1–8) each containing several sub-types (Agostini *et al*, 1997, 1998, 2000; Cubitt *et al*, 2001; Fernandez-Cobo *et al*, 2001; Jobes *et al*, 1998). These type specific differences have been invaluable for molecular anthropological studies of the migration patterns of ancient peoples (Agostini *et al*, 1997, 1998, 2000; Cubitt *et al*, 2001; Fernandez-Cobo *et al*, 2001; Jobes *et al*, 1998). The sequence polymorphisms in the coding sequences are for the most part silent mutations and are therefore not correlated with an increased risk of developing PML. Nonetheless several studies have found a correlation between JCV type 2 and PML (Agostini *et al*, 1998; Dubois *et al*, 2001). As typing of these isolates is performed by PCR amplification of the VP1 coding region some have

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speculated that differences in critical amino acids that define virus-receptor interactions may play a role in pathogenesis (Dubois *et al*, 2001). While this is an excellent suggestion and is based on solid data from the mouse polyomavirus literature (Dawe *et al*, 1987; Dubensky *et al*, 1991; Freund *et al*, 1991), to date, nobody has identified amino acid polymorphisms in the JCV capsid proteins (Kato *et al*, 2000). It is therefore difficult to imagine how silent mutations in the coding regions of JCV could alter the biology of the virus. In contrast, the highly variable noncoding region of the JCV genome is clearly compartmentalized and associated with disease progression (Agostini *et al*, 1997; Jensen and Major, 2001; Phister *et al*, 2001). For example, the archetype or type II-S JCV is the most commonly found sequence but it is not generally associated with PML. In contrast, the rearranged forms (type I-R or II-R) are strongly associated with PML and are also found in lymphoid organs and in circulating B cells (Jensen and Major, 2001). These types are rarely found in urine.

In this issue of the journal three papers shed further light on this subject. The first paper by Pagani *et al* describe the regional distribution of JCV genotypes in Italy. Surprisingly they find that both type 1 and type 4 are most prevalent and that type 2 and 3 are rare. This differs somewhat from previous reports in Europe where type 4 is not often seen. There were some regional variations in type with type 2 being more represented in the north than anywhere else in Italy. The authors also identified an unexpected high frequency of a new type 4 sub-type. The data suggest that genotypes may vary considerably between geographic areas within the same country. The second paper by Fedele *et al* studied the transcriptional control regions of JCV isolated from paired CSF, plasma, and urine samples of patients with PML. They hypothesized that if the plasma, CSF, and brain sequences were similar that this would indicate that the lymphoid organs were the major sites of viral rearrangement. After a careful and well-controlled study they did in fact confirm that plasma, lymphocytes, CSF, and brain all showed identical rearranged TCRs. All of the urine samples from these patients contained non-rearranged archetype forms of the virus. Finally O'Neill *et al* offer a mechanistic explanation for both the maintenance of archetype forms in the kidney and the evolution of rearranged forms in non-kidney tissue. In this manuscript, they show that rearranged forms of JCV (including a prototype Mad-1 strain) provide a helper function for the growth of archetype strains. This, however, comes at it's own expense as the archetypes limit the growth of the rearranged forms. These data predict that a small replicating pool of rearranged virus may actually be necessary for growth of archetype variants in the kidney. It is hypothesized that during periods of immune suppression that the rearranged forms can traffic to naive tissues and replicate unimpeded by archetype viruses. This is an intriguing hypothesis and if true it could explain why only a minority of immunosuppressed patients develop PML.

In summary, future efforts focused on characterizing biological differences between natural isolates of JCV should lead to a better understanding of the molecular pathogenesis of JCV induced disease. It will also be of interest to determine whether some strains of JCV harbor mutations that led to amino acid polymorphisms in the extracellular loops of VP1. This is of paramount importance as single point mutations in the capsid protein of mouse polyomavirus drastically alter receptor recognition, spread, and pathogenesis in the mouse (Freund *et al*, 1991).

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