Pathogenesis of Progressive Multifocal Leukoencephalopathy—Revisited

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Progressive multifocal leukoencephalopathy (PML) is a demyelinating disease of the central nervous system that rarely occurs even though the proven etiological agent of PML, the polyomavirus JC (JC virus), is ubiquitous within the human population. The common feature of PML cases appears to be underlying immunosuppression, and PML has gained clinical visibility because of its association with human immunodeficiency virus and AIDS and its occurrence as a side effect of certain immunomodulatory drugs. A hypothesis has gained general acceptance that JC virus causes a primary infection in childhood and enters a latent state, after which immunosuppression allows viral reactivation leading to PML. Nonetheless, many important aspects of PML pathogenesis remain unclear, including the molecular bases of latency and reactivation, the site(s) of latency, the relationship of archetype and prototype virus, and the mode of virus transmission within the body and between individuals. In this review, we will revisit these areas and examine what the available evidence suggests.
frequent occurring in 1%–10% of AIDS cases [18], with AIDS accounting for 55%–85% of PML cases [19]. The advent of novel immunomodulatory drugs has also illustrated the importance of the immune system in modulating JCV, with PML observed in patients receiving natalizumab [20, 21], rituximab [22, 23], and efalizumab [24].

Concerning the life cycle of JCV and the occurrence of PML in immunosuppressive states, a viewpoint has emerged that the following events occur. JCV is transmitted to an individual during childhood, establishes a primary viremia, is eliminated by the immune system, but then enters a “latent state” in the kidney. In this scenario, immunosuppression allows virus to reactivate, whereupon it can migrate to the brain and undergo genetic changes (neuroadaptation) that allow replication in glial cells and hence PML. We will examine the different aspects of this model and how well they are supported by available evidence. Central to unraveling these issues is the relationship between the 2 genetic forms of the virus, which differ in the NCCR, the key region in viral regulation because it controls early and late transcriptional and DNA replication. The archetypal form of the virus is found in kidney, urine, and sewage and is typified by the CY strain of JCV [25]. The prototypical form of JCV, also known as PML-type JCV, is associated with PML and is typified by the Mad-1 strain of JCV [26]. Relative to archetypal NCCR, prototypical Mad-1 JCV is characterized by 2 deletions and a duplication, as shown in Figure 2.

**TRANSMISSION OF JCV**

Primary infection by JCV is thought to be subclinical, occurring during childhood, as evidenced by the seroepidemiological evidence cited above. However, this simple statement masks 2 important unresolved issues. Firstly, it is not established whether the transmissible form of the virus is archetypal, prototypical, or both. Secondly, it is not known whether JCV superinfections can occur after initial childhood infection. It should be noted that the archetypal and prototypical forms of the virus differ only within the noncoding region and this will therefore not be reflected in any changes in the amino acid sequence and hence the antigenicity of viral proteins. Thus, superinfection events, in which an individual who is infected by one form of the virus becomes superinfected by the other, may not be detectable serologically.
The finding of JCV in the tonsils led to the proposal that tonsils may serve as an initial site of viral infection [27, 28]. In this scenario, virus might enter the mouth or nose by close interpersonal contact or via fomites. However, rather than being a portal of entry, it is also possible that JCV enters the tonsils via the bloodstream, because JCV can reside in B lymphocytes, as discussed below, and the tonsils may be a site of latency.

The discovery of archetypal virus with a simpler nonrepetitive NCCR [25] led to the hypothesis that this represented the transmittable form of JCV [29]. This is an attractive hypothesis for a number of reasons. First, the archetype contains all the genetic information necessary to give rise to the known PML types of JCV by the processes of deletion and duplication. Second, it is the only form of the virus that is found in urine of normal individuals. Yogo et al [30] analyzed 298 NCCR sequences from complete JCV genomes directly cloned from the urine of nonimmunocompromised individuals and found the archetypal configuration with only sporadic rearrangements, which were simple and short deletions or duplications in contrast to the complicated rearrangements in PML-type NCCRs. In addition, archetypal NCCR was reported in nearly all isolates of JCV from sewage samples from different geographical areas suggesting that archetype might be involved in transmission of virus by contaminated food, water, and fomites [31, 32].

Two portals of entry for JCV into the body have been suggested: the tonsils and the gastrointestinal (GI) tract (see below). As mentioned above, 2 reports have placed JCV in tonsil tissue [27, 28]. Both reports examined samples from multiple patients and were careful to sequence multiple clones of polymerase chain reaction (PCR) product DNA. Surprisingly, the analyses of the

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**Figure 2.** Comparison of prototypical progressive multifocal leukoencephalopathy (PML)-type Mad-1 strain of JC virus (JCV) with archetypal CY strain. The DNA sequences of the noncoding control region (NCCR) of Mad-1 and CY are shown aligned together, with Mad-1 on top in boldface and CY below in regular face. Numbering is relative to the Mad-1 strain (GenBank NC_001699, formerly J02226) [26]. The capitalized CAT (nucleotides 5011–5013) corresponds to the reverse complement of ATG start codon for T antigen and demarks the end of the early region and the start of the NCCR. The region at the 5' end of the NCCR (nucleotides 5014–5036) is identical for Mad-1 and CY and is very highly conserved in all strains of JCV. This area contains nucleotide 1 of the 5130–base pair (bp) JCV Mad-1 circular genome. The underlined sequence (nucleotides 5111–5129) contains the origin of DNA replication, including the GGA/GGC-rich element (nucleotides 5118–5132) and the A/T-rich element (nucleotides 15–29). The 23-bp element that is deleted in Mad-1 (compared with CY, between nucleotides 36 and 37) is indicated by a single asterisk and highlighted in green. The 66-bp element deleted in Mad-1 (compared with CY, between nucleotides 84 and 85) is indicated by a double asterisk and highlighted in blue. The sequence of the 23- and 66-bp deletions is shown at the bottom of the figure. The region containing the deletions (nucleotides 12–109) is duplicated in Mad-1; this is known as the 98-bp tandem repeat and is highlighted in yellow (nucleotides 12–207). The junction between the two 98-bp repeats is shown by brackets, highlighted in red. The 3′ end of the NCCR (nucleotides 208–276) is identical for Mad-1 and CY. The capitalized ATG (nucleotides 277–279) corresponds to the ATG start codon of agnoprotein and demarks the end of the NCCR and the start of the late region.
JCV NCCR DNA sequences yielded very different results with important implications for understanding viral transmission.

Monaco et al [27] tested 54 tonsils, 38 from children and 16 from adult donors, and detected JCV DNA in 21 (39%), using PCR with NCCR primers. DNA extracted from children’s nondissected tonsil tissue, isolated tonsillar lymphocytes, and isolated stromal cells nearly all contained tandem repeat PML-type arrangements, with only a few clones having archetypal structure. From these data, it was argued that the PML-type of JCV was the infectious form, which entered the tonsil, and that the archetype represents a postinfection, in vivo adaption [27, 33]. However, this model does not seem plausible because the archetype contains genetic material (the 66- and 23-bp “insertions,” see Figure 2) not found in PML-type virus.

Kato et al [28] detected JCV NCCR DNA in tonsil tissue from 14 (44%) of 32 donors with tonsillitis and tonsillar hypertrophy. However, sequencing indicated that they were archetypal or, in a few cases, with slight deviations. From these data, it was suggested that tonsil tissue is the site of initial JCV infection by archetypal strain circulating in the human population. Even if this is the case, it is difficult to explain why no PML-type JCV was detected at all, given that it has been detected in B lymphocytes (see below), which are present in the tonsil.

It is not clear why these 2 important studies had such disparate results, nor is it possible to judge whether they reflect real differences between the 2 groups of patients (the first group from the United States and the second from Japan) or methodological problems associated with PCR. More studies are clearly warranted on JCV in tonsillar tissue, because this is of key importance in understanding viral transmission.

Finally, infection through the digestive tract is another possibility. Detection of JCV genomic sequences in epithelial cells from the GI tract [34, 35] and in the esophagus [36] suggests infection through the digestive tract. Ricciardiello et al [37] found PML-type Mad-1 to be the exclusive JCV strain present in the human colon. In this study, differences in the JCV NCCR isolated from colon cancer tissues and nonneoplastic epithelium were evaluated. After sequencing of 54 clones, no archetypal JCV was found and the only JCV strain detected in the human colon was Mad-1. Interestingly in this study, cancer tissue clones of JCV were found to have a deletion of 1 of the Mad-1 98-bp tandem repeats. Although findings are consistent with the GI tract’s being a site of infection via direct entry of ingested virus through the apical membrane of epithelial cells, alternatively, JCV may enter the gut epithelium indirectly from the bloodstream, as noted above for tonsils.

**PRIMARY VIREMIA**

The differences between the ages of seroconversion for JCV and BKV (Figure 1) indicate that these viruses are transmitted independently in the population and establish different initial primary infections. Further, early epidemiological studies discovered rare isolated populations, such as the Ewarhoyana Indians in 1970 Brazil, who were seronegative for both BKV and JCV, and the Tjitak linguistic group in 1969 West New Guinea, who were seropositive for BKV but seronegative for JCV [13, 38], which also underlines the independent transmission of these 2 closely related polyomaviruses and suggest that they are antigenically distinct.

As noted, it remains to be established whether archetype, prototype, or both are transmitted and establish the primary infection. This is important, because archetype and prototype viruses are antigenically identical. In this regard, it is possible that more than one JCV infection event can occur; that is, there may be a superinfection event with a different JCV type occurring after the initial childhood infection. This should be kept in mind when considering possible models of viral latency and reactivation, as discussed in the next section.

**LATENT STATE**

It is widely accepted that once the primary childhood viremia has been eliminated by the immune system, virus remains in the body in a state referred to as latency. The distribution of latent virus in different tissues around the body is thought to occur during the primary viremia. The latent state of JCV is not well understood but is thought to involve an asymptomatic, chronic, persistent infection wherein JCV DNA can be detected by highly sensitive PCR techniques but expression of JCV proteins cannot be detected by immunohistochemistry or Western blot analysis. Because JCV DNA but not protein is detected [7, 10, 11, 30], it is possible that this represents a true state of latency (ie, transcriptionally inactive virus). Presumably, the circular viral genome is present as an episome (latency), or alternatively viral DNA replication may occur sporadically or intermittently at a level below the threshold of detection (persistence), and this may depend on the tissue. In this regard, it has been shown by electron microscope studies of cells in culture that the closely related polyomavirus SV40 can replicate and virions can migrate to the plasma membrane and egress cells without causing cell lysis [39]. Many tissues have been reported to harbor latent JCV, including kidney [25], tonsil [27, 28], and peripheral blood leukocytes [40]. Importantly, it has been reported that JCV can be present in the brain of healthy individuals who do not have PML [41–46]. It is important to note that the virus is not thought to be replicating in non-PML brain, because expression of VP1 is undetectable although T antigen may be expressed in some malignant tissues.
[7, 10, 11, 36]. In the case of lymphoid tissues, it is not clear if latent virus is able to replicate. An alternative explanation for observation of viral association with lymphoid tissues and cells could be adherence of the virus to the sialic acid structures expressed on B cell surface or uptake of virus into phagosomes rather than true infection of these cells. In the case of the kidney, active viral replication is probably occurring episodically in the urothelium, because archetypal virus can sometimes be detected in the urine [25, 30]. It is instructional to examine the configurations of the NCCR of the virus that have been reported in these different tissues.

Archetypal JCV is the exclusive form found in kidney of normal individuals (Table 1) and is thought to replicate episodically or at low levels to give rise to virus shed in the urine and detected by PCR in urine samples. As noted, polyomaviruses may be released without cell lysis, so viral excretion may occur without any associated pathological damage. SV40 has been shown by EM studies to egress polarized kidney epithelial cells in culture via the apical, but not the basal cell surface [39].

In the brain, several groups have reported JCV in normal non-PML brain tissue. Elsner and Dörries [39] examined brain autopsy material from 67 individuals with disorders other than PML and demonstrated full-length JCV genomes in ~20% of the patients by Southern blot analysis. Mori et al [45] examined 91 autopsy brain tissue sections from 33 elderly patients without PML by PCR and Southern blot analysis after DNA extraction and detected JCV DNA in 15 sections from 10 patients. Indeed, in situ hybridization and immunohistochemistry for JCV DNA and capsid protein respectively indicated the presence of subclinical areas of JCV replication presenting as tiny punched demyelinated foci in the brains of 4 of 10 elderly patients [44]. It is possible that such foci represent the initiation of JCV replication and are subclinical precursors to PML lesions. Perez-Liz et al [46] detected JCV DNA in brain from 7 immunocompetent individuals without PML, although no viral proteins were detectable by immunohistochemistry. In this study, laser-capture microdissection showed the presence of JCV DNA in oligodendrocytes and astrocytes, but not in neurons. These findings suggest that the normal brain may be a site of viral latency, and thus JCV reactivation events may involve factors acting directly on the glial cells, as discussed in the next section. At least 2 studies have analyzed the configuration of the JCV NCCR in the normal brain, and both found it to be PML type (Table 1).

In the bloodstream, JCV can be present in a latent state in certain type of peripheral blood leukocytes including B lymphocytes (see Gallia et al [57] for a review of early studies and Berger et al

### Table 1. NCCR Configuration by Tissue Site in Subjects with or without Progressive Multifocal Leukoencephalopathy (PML)

<table>
<thead>
<tr>
<th>Subjects</th>
<th>NCCR Configuration</th>
<th>Kidney</th>
<th>PBMCs</th>
<th>Bone Marrow</th>
<th>Tonsils</th>
<th>Brain</th>
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<tbody>
<tr>
<td>Subjects without PML</td>
<td>Archetype</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
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<tr>
<td>PML type</td>
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**NOTE.** a Data represent the presence (plus signs) or absence (minus signs) of the archetypal and PML-type (rearranged) configurations of JC virus (JCV) noncoding control region (NCCR) in various tissues from subjects with or without PML. ND, no data; PBMCs, peripheral blood mononuclear cells.

b The archetypal arrangement of the JCV NCCR was first reported in urine by Yogo et al [25]. For review, see Yogo and Sugimoto [29]. White et al sequenced cloned amplified DNA from non-PML kidney tissue sections and found archetypal JCV [41]. In a more extensive study, Yogo et al sequenced 298 clones from normal urine, and all were found to be archetypal, although sporadic small rearrangements were occasionally detected [30].

c Ciappi et al [47] observed archetypal JCV in non-PML PBMCs by cloning and sequencing of polymerase chain reaction (PCR) product.

d Tan et al analyzed human immunodeficiency virus (HIV)-negative, HIV-positive, and HIV-positive, PML-positive bone marrow aspirates and archival bone marrow [48]. PCR products were cloned, and 10 individual clones/amplifications were sequenced. All were found to be PML type. Of note, clones were derived from 6 HIV-positive and 1 HIV-negative patient sample, and all 7 had the Mad-1 configuration. However, each patient sample contained unique point mutations, either in the first and/or second 98-base pair (bp) repeat element or in the adjacent agnogene.

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There are many gray areas in our understanding of the biology of JCV. Perhaps of most importance are issues related to mechanisms whereby latent JCV is reactivated, because these lead to PML and thus have therapeutic implications. Berger et al [58] have argued that the rarity of PML compared with the ubiquity of infection means that there are probably multiple barriers to the development of PML and more than one must be breached for PML to occur. No clear, generally accepted model for JCV reactivation has emerged, but here we will discuss possibilities for what these barriers are and how they are circumvented by during PML pathogenesis.

Because JCV DNA has been detected in the brains of normal individuals, we have favored a model where latent JCV in the brain is reactivated. The JCV NCCR contains binding sites for transcription factors regulated downstream of cytokine signal transduction pathways, including NF-κB [59–62], AP-1 [63], Egr-1 [64], and C/EBPβ [62]. In this scenario, virus reactivates transcription in response to extracellular cytokines initiating a “flare-up” of viral replication. From this point, virus might spread and form a PML lesion, owing to a lack of immunosurveillance associated with the underlying immunosuppression. In PML occurring with human immunodeficiency virus type 1 (HIV-1) or AIDS, HIV-1 transactivator protein Tat may also have a role, because Tat can stimulate JCV transcription [65] and replication [66].

Other models of JCV reactivation emphasize the role of cells of the immune system [58, 67]. In this respect, the immune system probably has 2 important roles. First, as discussed above, immune cells, especially B lymphocytes, may be sites of JCV latency and this latent virus may be PML-type JCV [33, 40, 57]. Clearly, these cells may not only serve as a source of latent virus but may also allow virus to circulate around the body and enter the brain. Second, cytotoxic CD8 T cells are important for eliminating infected cells and controlling viral spread, that is, immunosurveillance [68]. A reduction in immunosurveillance may explain why natalizumab, which prevents T lymphocytes from crossing the blood-brain barrier, is associated with PML [21].

If there are multiple barriers to development of PML, there is no reason for exclusivity or inconsistency between different models. The exact cause for JCV reactivation and PML development may depend on the nature of immunosuppression and patient-specific factors. For example, in younger patients receiving immunomodulatory monoclonal antibodies, JCV mobilization to brain from periphery may be important, whereas in older patients, JCV may have already entered the brain. Here, reactivation of latent virus may be important, along with lack of immunosurveillance. Mori et al [44, 45] reported subclinical areas of JCV replication presenting as tiny punched demyelinated foci in brains of some elderly patients without PML.

**BILOGICAL DIFFERENCES BETWEEN ARCHETYPE AND PROTOTYPE**

A few studies have addressed how the rearrangement of the JCV NCCR affects the pathogenicity of JCV. One study described the negative effect of archetype-specific 23- and 66-bp sequences and lack of tandem duplication (Figure 2) on transcription in glial cells [69]. In another recent study, a side-by-side comparison of archetype and prototype transcription was performed, using a fluorescent protein reporter system in a variety of cell types [70]. Diverse PML-type NCCRs were found to enhance early gene expression compared with archetypal virus. Thus, the rearrangement of the NCCR probably increases the replication and cytopathology of JCV. Interestingly, archetypal JCV (but not PML-type JCV) failed to replicate in human kidney cultures [69], and PML-type JCV showed stronger early gene expression in the human kidney. Thus, the basis for the tropism of archetypal virus to kidney remains unexplained.

**CONCLUSIONS**

There are many holes in our knowledge of JCV biology, especially concerning transmission of virus, nature and site of viral latency, and mechanisms of virus reactivation and PML onset. However, other aspects seem to be clear, with findings that have become generally accepted. Chief among these is the concept that there are 2 forms of the virus: archetype and PML type. The archetype is the form always found in kidney and urine, and PM-type is the form always found in brain and PML. PML-type JCV, by virtue of the deletion of negative control elements and/or the duplication of positive control elements, is a more
active viral variant, with the pathogenic potential to cause glial cell lysis and PML [69]. Furthermore, PML-type JCV exists in peripheral blood cells in individuals without PML and so is a likely precursor of virus that will enter the brain.

What is the origin of the PML-type JCV in peripheral blood cells? PML-type virus may be transmitted between individuals and enter via the gut or tonsils and then subsequently infect peripheral blood cells. Alternatively, it may arise by genetic rearrangements (deletions and duplications) of a transmitted archetypal virus, either within the blood cell or at another site followed by entry into the blood. This speaks to the heart of the matter: the relationship between archetypal and PML-type virus. This has been debated for some time. For example, from the observations that the number of PML types is restricted and the Mad-1 NCCR is prevalent in the United States, Elsner and Dörries [71] argue that it is unlikely that PML-type JCV subtypes are generated anew in each individual during the course of infection. On the other hand, Newman and Frisque [72] argued that alternate explanations could be offered for these observations, such as the occurrence of rearrangement by a random mechanism, followed by the subsequent emergence of certain rearranged variants (eg, Mad-1) that arise because they have a replicative advantage and become the predominant form. Because JCV is phylogenetically a single species and because novel variants of PML-type NCCR continue to be reported, it is clear that an unknown mechanism for viral rearrangement must be at play. However, the question of the relationship of this rearrangement to virus transmission and the acquisition of PML-type JCV by an individual remains unanswered. It is possible that both archetypal and PML-type virus are transmissible and that superinfection is not detected because they are antigenically identical.

Whatever the origin of circulating virus, downstream events may be more important from a therapeutic point of view; these include reactivation of the virus, lytic infection of glial cells in the brain, failure of immunosurveillance, and the onset of PML. The are significant differences in opinion as to how this occurs. Importantly, although JCV may be detected in a latent state in many tissues, it is not clear which of these sites represents “functional latency,” yielding a virus that can subsequently cause PML [67]. Nonetheless, JCV must migrate from blood to brain and establish a productive lytic infection that can develop into a PML plaque and escape immunosurveillance. Any and all of these stages may provide targets for developing novel treatments for PML, a disease that remains a significant public health threat in dire need of effective therapy.

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References


