Review: JC Virus Infection of Lymphocytes—Revisited

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JC virus (JCV), the causative agent of the fatal human demyelinating disease progressive multifocal leukoencephalopathy (PML), is an opportunistic papovavirus that infects and destroys oligodendrocytes, the myelin-producing cells of the central nervous system. Since its isolation from the brain of a PML patient, JCV has long been classed as a neurotropic virus. Many studies, however, have demonstrated that JCV can infect various other cell types, including immune system cells. Moreover, several recent studies have focused specifically on lymphocytes as a target of JCV. This review chronicles the association of JCV with lymphocytes, including cell type localization, molecular regulation, and viral sequences, and discusses clinical implications of these findings.

The opportunistic polyomavirus, JC virus (JCV), is the etiologic agent of the subacute human demyelinating disease, progressive multifocal leukoencephalopathy (PML) (reviewed in [1, 2]). Classically, PML presents as a triad of symptoms: visual deficits, motor weakness, and altered mental state [3]. Less frequently, PML patients may display speech dysfunction, cerebellar disorders, sensory deficits, extrapyramidal syndromes, headache, seizures, and vertigo [1, 3]. The neurologic signs and symptoms of PML result from the viral destruction of myelin-producing oligodendrocytes in the central nervous system (CNS). The cardinal pathologic features of PML include multiple foci of myelin and oligodendrogial cell loss, hyperchromatic enlarged oligodendroglial nuclei, and bizarre astrocytes with enlarged multilobulated nuclei. Initial areas of demyelination are small and multiple but usually progress, with coalescing foci developing into lesions several centimeters in diameter. The widespread and multifocal distribution of the demyelinating lesions suggests a hematogenous viral spread to the CNS.

JCV was originally cultivated by inoculating primary human fetal glial cells (HFGC) with postmortem brain extracts derived from a PML patient (initials J.C.) [4]. HFGC remain the most susceptible host cell for JCV, which has led to the classification of this papovavirus as neurotropic. As such, much of the cellular and molecular biology of JCV has been studied in glial cells. Over the years, many studies have demonstrated that JCV can infect various other cell types (reviewed in [5]). Recently, lymphocytes have become a cell type of interest in JCV biology with the demonstration of JCV infection of B cells in patients with PML [6]. Here we chronicle the association of JCV with lymphocytes, with emphasis on cell type localization, gene regulation, and viral sequence assessment.

JCV Association with Lymphocytes

Perhaps the first association of JCV DNA with lymphocytes was suggested by Grinnell et al. [7]. These authors, using Southern blot analysis for JCV DNA and indirect immunofluorescence for virion capsid and large T antigen, investigated the extraneural tissue distribution of JCV in postmortem specimens from 10 patients with PML. Although JCV proteins could not be detected in any extraneural tissues investigated, JCV DNA was detected in liver, lung, lymph node, and spleen tissues from 2 children with severe combined immunodeficiency syndrome and in lung tissue from an adult patient with Hodgkin’s disease. Although the cell type(s) responsible for harboring JCV was not identified in these PML patients, the tissues containing JCV DNA have circulating lymphocytes that could have been the source of the viral DNA.

The first report demonstrating JCV in lymphocytes came in 1988. Houff et al. [6] described the presence of JCV DNA and virion capsid antigen in bone marrow mononuclear cells isolated from 2 PML patients. In the first patient, who also had AIDS, JCV DNA and capsid antigen were found in bone marrow mononuclear cells by in situ hybridization and immunocytochemistry, respectively. In the second patient, who was reported to have no underlying immunosuppression, JCV DNA and capsid antigen were found in mononuclear cells from bone marrow aspirates and biopsy specimens. These JCV-infected cells were identified as κ light chain–bearing B lymphocytes. Moreover, this study also reported the presence of JCV in mononuclear cells located within the CNS perivascular spaces. These mononuclear cells were demonstrated to contain JCV DNA and virion capsid antigen by in situ hybridization and immunocytochemistry, respectively.
Together, these data provided the first evidence that JCV can infect mononuclear cells and, more specifically, B lymphocytes. Since this original description, JCV has been demonstrated in lymphocytes present in the bone marrow, CNS, and peripheral blood (table 1).

Several studies have detected JCV DNA in mononuclear cells in the bone marrow and the CNS [8–11]. Tornatore et al. [9], using in situ hybridization, demonstrated the presence of JCV DNA in mononuclear cells isolated from the bone marrow in 5 (31%) of 16 PML patients. A study by Schneider and Dorries [10], using polymerase chain reaction (PCR) amplification followed by Southern blot analysis, detected JCV sequences in bone marrow mononuclear cells in patients with leukemia before and after bone marrow transplantation. Additionally, Katz et al. [11], using in situ hybridization, detected JCV DNA in bone marrow biopsy specimens from a 15-year-old boy with PML complicating Wiskott-Aldrich syndrome. Moreover, Major et al. [8], using in situ hybridization, reported the presence of JCV DNA in mononuclear cells in brain tissue from a PML patient. These JCV-positive cells were shown to be B lymphocytes (CD45R+ cells) by dual-labeling techniques.

Table 1. Association of JCV with cells of the immune system.

<table>
<thead>
<tr>
<th>Tissue/organ, cell type(s)</th>
<th>Detection method(s)</th>
<th>No. JCV-positive/total no.</th>
<th>Underlying condition(s)</th>
<th>Reference</th>
</tr>
</thead>
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<tr>
<td>Brain</td>
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<tr>
<td>Mononuclear cells</td>
<td>In situ hybridization and immunocytochemistry</td>
<td>2 case reports (29- and 53-year-old men)</td>
<td>PML, 1 also had AIDS; other had no underlying disease</td>
<td>[6]</td>
</tr>
<tr>
<td>B lymphocytes (CD45R+)</td>
<td>In situ hybridization</td>
<td>1/1</td>
<td>PML</td>
<td>[8]</td>
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<tr>
<td>Bone marrow</td>
<td></td>
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<tr>
<td>Mononuclear cells and B lymphocytes (κ chain+)</td>
<td>In situ hybridization and immunocytochemistry</td>
<td>2 case reports (29- and 53-year-old men)</td>
<td>PML, 1 also had AIDS; other had no underlying disease</td>
<td>[6]</td>
</tr>
<tr>
<td>Mononuclear cells</td>
<td>In situ hybridization</td>
<td>5/16</td>
<td>PML</td>
<td>[9]</td>
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<tr>
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<td>PCR/Southern</td>
<td>3/3</td>
<td>Leukemia</td>
<td>[10]</td>
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<tr>
<td>NR</td>
<td>In situ hybridization</td>
<td>Case report (15-year-old boy)</td>
<td>PML, Wiskott-Aldrich syndrome</td>
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<tr>
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<td>PCR/Southern</td>
<td>17/19</td>
<td>PML, 17 also had AIDS</td>
<td>[9]</td>
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<td>HIV-1–positive</td>
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<td>Parkinson’s disease</td>
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<tr>
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<td>[12]</td>
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<tr>
<td></td>
<td></td>
<td>9/11</td>
<td>Huntington’s disease</td>
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<td></td>
<td>15/18</td>
<td>Healthy</td>
<td></td>
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<tr>
<td>Mononuclear cells</td>
<td>PCR/Southern</td>
<td>Case report (59-year-old man)</td>
<td>PML, CLL, EBV cerebral infection, cerebral parenchymal infiltration</td>
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<td>39/135</td>
<td>HIV-1–positive, 5 also had PML</td>
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<td>HIV-1–negative, immunosuppressed</td>
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<td>BMT patients</td>
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<td></td>
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<td>AIDS patient</td>
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<td>14/36</td>
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<td>B lymphocytes (CD19+)</td>
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<td>1/2</td>
<td>2 AIDS patients, 1 with PML</td>
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<td>4/5</td>
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<td>[18]</td>
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<td>PML, some HIV-1–positive</td>
<td>[19]</td>
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<tr>
<td></td>
<td></td>
<td>0/10</td>
<td>AIDS</td>
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</table>

NOTE: BMMC = bone marrow mononuclear cells; PML = progressive multifocal leukoencephalopathy; PCR = polymerase chain reaction; NR = not reported; PBL = peripheral blood lymphocytes; PBMC = peripheral blood mononuclear cells; BMT = bone marrow transplant; HIV = human immunodeficiency virus; CLL = chronic lymphocytic leukemia; EBV = Epstein-Barr virus.
Because JCV has been detected in lymphocytes present in both bone marrow aspirates and biopsies [6, 9–11] as well as in brain specimens [6, 8], it is not surprising that JCV has also been detected in peripheral blood lymphocytes (PBL) [9, 11, 12–15]. Tornatore et al. [9] utilized PCR amplification followed by Southern blot analysis to investigate the presence of JCV DNA in PBL and reported JCV DNA in 17 (89%) of 19 PML patients, 17 of whom also had AIDS. In this study, the presence of JCV was also investigated in 2 other patient populations: 26 non-PML human immunodeficiency virus type 1 (HIV-1)–seropositive patients and 30 patients with Parkinson’s disease. Although JCV was not detected in any of the patients with Parkinson’s disease, JCV DNA was detected in 10 (38%) of 26 HIV-1–positive patients without PML.

Several other groups have demonstrated JCV in PBL. Using PCR amplification followed by Southern blot analysis, Dorries et al. [12] detected JCV DNA in PBL from 3 patients with PML. Moreover, they detected JCV DNA in peripheral blood mononuclear cells (PBMC) of immunocompetent individuals; JCV DNA was detected in PBL from 15 (83%) of 18 healthy adults and from 9 (82%) of 11 patients with Huntington’s disease. Katz et al. [11] detected JCV DNA in PBL from a 15-year-old boy with PML and Wiskott-Aldrich syndrome. Farge et al. [13], using PCR amplification followed by Southern blot analysis, detected JCV DNA in peripheral blood mononuclear cells in an HIV-1–seronegative patient who had B cell chronic lymphocytic leukemia and simultaneous PML, diffuse cerebral leukemic parenchymal infiltration, and latent Epstein-Barr virus (EBV) cerebral coinfection. Using PCR amplification followed by either Southern blot analysis or a liquid phase hybridization assay, Dubois et al. [14] detected JCV DNA in 39 (29%) of 135 PBL samples from HIV-1–infected immunocompromised persons and in 10 (16%) of 61 PBL samples isolated from HIV-1–negative immunosuppressed patients. Azzi et al. [15], using nested PCR and Southern blotting, reported the detection of JCV in PBL from 3 (9%) of 33 bone marrow transplant patients, 15 (47%) of 32 patients with AIDS, and 14 (39%) of 36 healthy persons.

Monaco et al. [16] examined PBMC from 2 AIDS patients, 1 who was clinically diagnosed with PML and a second patient without PML. In this study, PBMC were sorted into T cells (CD3+), B cells (CD19+), and CD34+ cells by flow cytometry and analyzed for the presence of JCV by PCR amplification followed by Southern blot analysis. JCV DNA was detected in the unsorted PBMC and the sorted B cell subpopulations from the PML patient; there was no JCV DNA in the T cell population from the PML patient and none in the T, B, or unsorted population from the non-PML patient. This study not only demonstrates that JCV is present in lymphocytes but also corroborates previous studies [6, 8], suggesting that there may be a subpopulation of lymphocytes, specifically B cells, with which JCV associates. Although these studies [6, 8, 16] suggest that JCV may be associated with a subset of the lymphocyte population, the selective presence of JCV within B cells has only been demonstrated in a few cases, and in fact, another report indicated that JCV may be present in both B and non-B cells [20]. Indeed, larger studies are necessary to further define the lymphotropic specificity of JCV.

In contrast to the above reports, there have been a number of studies unable to detect JCV DNA in PBL or PBMC [17–19]. Using PCR amplification and Southern blotting, Quinlivan et al. [17] could not detect JCV DNA in 10 peripheral blood specimens from HIV-1–positive patients. Sundsfjord et al. [18] were unable to detect JCV DNA in PBL of 42 HIV-1–positive patients using a nested PCR amplification reaction followed by Southern blotting. A study by Perrons et al. [19], using similar techniques, was unable to detect JCV DNA in PBL from patients with or without PML.

Taken together, the above studies demonstrate that JCV-containing lymphocytes can be detected in patients irrespective of their immunocompetence. It is unclear why there is so much variation when comparing the percentage of a given population that contains JCV in PBL. Such discrepancies, however, may be attributable to patient sampling, sample preparation, or the methods used for detection. Nonetheless, evidence is accumulating to support lymphocytes as a target of JCV.

Infection of Lymphocytes

The presence of JCV DNA in lymphocytes isolated from bone marrow, brain, or peripheral blood does not address whether or not JCV can productively infect these cells. In fact, the presence of DNA replication and capsid antigen is only suggestive of a productive infection. In vitro experiments, however, have shown that JCV is indeed capable of productively infecting lymphocytes [16, 21]. Atwood et al. [21] demonstrated that JCV is able to multiply in tissue culture B cell lines such as Namalwa, BJAB, and LyT3. Moreover, these JCV-infected B cells were able to produce infectious progeny virions that could subsequently infect HFGC.

A recent study by Monaco et al. [16] demonstrated that a variety of cells, including both primary and established cell lines, are susceptible to JCV infection. In this study, hematopoietic progenitor cell (CD34+) lines KG-1 and KG-1a were susceptible to JCV infection; primary CD34+ cells isolated from human fetal liver were also susceptible to JCV infection. KG-1 cells can be differentiated into mature macrophages upon phorbol ester treatment. These differentiated macrophages and the promonocytic cell line, U937, were not susceptible to JCV infection. These data support the lymphoid cell susceptibility observed in the various studies discussed above. Monaco et al. [16] also demonstrated that primary B cells (CD19+) isolated from both peripheral blood and tonsillar tissues were susceptible to JCV infection as well. Moreover, the KG-1a, primary CD34+ cells, and primary B lymphocytes were all shown to produce infectious virus capable of infecting HFGC. It should be noted that only a low percentage of immune system cells (1%–5%) are capable of being infected with JCV. This is
~15 times lower than the percentage of human fetal glial cells infected by JCV (30%–50%). Nonetheless, these studies demonstrate that JCV can indeed productively infect established tissue culture B cell lines, primary B cells, and primary hematopoietic progenitor cells.

Of interest, human tonsillar stromal cells are also susceptible to JCV infection [16]. Stromal cells derived from tonsil tissue have a greater rate of JCV infectivity (~20%) than B cells, which could be attributed to the expression of specific transcription factors, such as class B nuclear factor-1 (NF-1), that increase efficiency of viral replication (Major EO et al., unpublished observations). The significance of tonsillar stromal cell infection in the pathogenesis of PML is addressed in the discussion.

**Molecular Regulation in Lymphocytes**

Since HFGC are the most susceptible host cell for JCV, most studies focusing on the molecular regulation of this virus have involved glial cells (reviewed in [22]). Although information about the regulation of JCV in lymphocytes is modest in comparison, several interesting comparisons can be made. Major et al. [8] demonstrated that both HFGC and B cells contain nuclear protein(s) that interact with specific sequences in the regulatory region of JCV. Atwood et al. [21], using DNase I footprint analysis, demonstrated that nuclear proteins present in two B lymphocytic cell lines (Namalwa and LyT3) protected the same sequences within the JCV regulatory region as proteins present in glial cells. The significance of this finding, however, is clouded by the observation that nuclear extracts from HeLa cells also protected the same region of JCV. Using electrophoretic mobility shift assays (EMSA) with the same regulatory sequence of JCV, Atwood et al. [21] demonstrated that the gel shift patterns from nuclear extracts obtained from both B cell lines were similar to one another but distinct from the pattern observed with HeLa nuclear extract. Competition analysis using an oligonucleotide containing an NF-1 binding site specifically eliminated a single complex present in both B cell extracts but competed for a different complex in the HeLa cell extract. Likewise, a mutated NF-1 oligonucleotide failed to compete for the formation of any complexes obtained with either B cell extract but did compete for a complex obtained with the HeLa cell extract. These experiments suggest that there may be factors common to both glial and B cells that interact with the regulatory region of JCV.

Rieckmann et al. [23] also investigated the presence of a factor present in both glial and B cells. Using EMSAs with an oligonucleotide derived from the regulatory region of JCV (nt 130–160, domain B), specific bands of the same mobility were detected in nuclear extracts from human fetal glial cells, U-251 glioma cells, a B cell line (BJAB), and in vitro–activated tonsillar B lymphocytes but not from T lymphocytes. Additionally, a specific shift was detected in nuclear extracts from primary tonsillar or lymph node B cells from 5 AIDS patients.

Fine mapping of the binding of this protein to domain B revealed that the first of two TGGC tetranucleotide repeats was involved in binding of this factor. UV cross-linking experiments demonstrated the presence of a 46-kDa DNA-protein complex from BJAB, HFGC, and B cells from an AIDS patient. Transient transfection experiments revealed that this B region was active in B lymphocytes and glial cells but not in T lymphocytes. Mutation of the TGGC repeats not only abolished binding to this region but also decreased the activity of this region. These experiments suggest that the interaction of this factor with the regulatory region of JCV is of functional significance in the expression of JCV in both B lymphocytes and glial cells.

**Sequences in Lymphocytes**

Unlike most of the viral genome, the promoter/enhancer region of JCV differs among the various isolates [24]. On the basis of the differences within the viral regulatory region, JCV has been classified into several types: types I, II, and archetype (reviewed in [25]). The regulatory region of type I virus has a 98-bp tandem repeat, each containing a TATA box adjacent to a pentanucleotide repeat. The first JCV isolate sequenced [26], Mad-1, belongs to this class. JCV type II genomes differ slightly from one another but share several features. The control region of type II strains lacks the distal TATA sequence and usually contains a 23-bp GC-rich insertion within the proximal repeat. The Mad-4 JCV strain differs from this classification; it has a deletion in the TATA sequence but lacks the 23-bp insertion usually found in type II strains. Types I and II genomes have been isolated from both the brain and urine of PML patients. Other types of JCV genomes, types III and IV, have been described [27, 28]. An “archetype” JCV genome has also been described [29], which consists of a single 98-bp repeat with the 23-bp GC-rich insert and a second 66-bp insert. Archetype genomes have been isolated from the urine of many patients, including renal transplant patients [29], pregnant women [30], and AIDS patients [31]. Because this JCV strain contains all of the elements found in both type I and II genomes, it has been postulated that all rearranged types of JCV are adaptations of this archetype strain [29].

There have been several types of JCV detected in lymphocytes [9, 12, 15]. Tornatore et al. [9] sequenced the regulatory region of JCV isolated from peripheral lymphocytes of 3 patients, 2 of whom were PML patients with AIDS; the third was a JCV-positive HIV-1–seropositive patient without PML. The prototype Mad-1 strain (type I) was found in 1 PML patient with AIDS, a Mad-4 strain was found in the second PML patient with AIDS, and a Mad-4 strain with a 1-nucleotide transversion was found in the JCV-positive HIV-1–seropositive patient without PML. Dorries et al. [12] reported the sequence of the regulatory region of JCV isolated from PBL of 6 immunocompetent patients. In all cases, the sequence was that of Mad-1 (type I): one had a 4-bp insertion and two others...
had 3 point mutations. Azzi et al. [15] reported the presence of both rearranged types as well as archetype JC virus sequences in PBL. Although this study used restriction enzyme digestion to classify the genomes of JCV in the lymphocytes, it is noteworthy in light of the fact that archetype genomes are almost exclusively found in kidney tissue and urinary JCV isolates.

Discussion and Clinical Implications

Seroepidemiologic studies demonstrate that infection with JCV is very common and usually occurs during childhood. In fact, >80% of the human adult population is seropositive for JCV specific antibodies [32, 33]. Despite this high prevalence of infection, JCV-induced disease is rare, occurring almost exclusively in individuals with immune suppression [1]. Because of these observations, JCV is thought to establish a latent infection and become reactivated upon immune suppression [5]. Lymphocytes offer attractive candidates for JCV latency and reactivation. Studies summarized here support the ability of B lymphocytes to support JCV replication. Several features about B lymphocyte growth and differentiation and the background in which PML develops lead to possible mechanisms for viral latency and reactivation. Of particular interest are the many underlying diseases associated with PML that are characterized by polyclonal lymphocyte activation [1, 34, 35]. Activated lymphocytes can cross the blood-brain barrier without requiring antigen recognition at the cerebrovascular endothelial surface. These findings provide a means by which activated JCV-infected B lymphocytes could enter the brain and in turn permit JCV to lytically infect oligodendrocytes, inducing CNS demyelination. Moreover, the presence of replicating JCV DNA in perivascular cells and B lymphocytes in the brains of PML patients [6, 8] provides in vivo evidence that JCV replication in B lymphocytes may be a necessary, if not sufficient, event in the pathogenesis of PML.

The proposed infection of the CNS by JCV-infected B lymphocytes is not without precedent. Viral infection and replication in hematogenous cells is well known. Virus-infected mononuclear cells are believed to be a source of infection of the CNS in a number of nervous system diseases including those caused by HIV, cytomegalovirus, and EBV. Results presented here suggest B lymphocytes infected with JCV may be another mononuclear cell infection that leads to CNS infection.

The observation that human tonsillar stromal cells can be infected with JCV raises interesting speculations about the primary infection. If primary infection occurs via a respiratory route, perhaps tonsillar stromal cells, because of their relatively higher susceptibility to JCV infection (only 2.5 times less susceptible that HFGC), could be the initial cell type JCV infects. Moreover, stromal cells are a major component of lymphoid tissues within the body and have been shown to interact with B lymphocytes [36]. Thus, tonsillar stromal cells could also provide a reservoir for lymphocyte infection, which could seed the bone marrow and other lymphoid organs.

The relationship between JCV and lymphocytes is strengthened by observations from other polyomaviruses. BK virus (BKV), although isolated from urinary tract epithelial cells, has also been shown to be lymphotropic. In fact, the presence of virus receptors was demonstrated on human peripheral B lymphocytes [37]. Moreover, BKV has also been shown to replicate in human lymphocytes isolated from peripheral blood [38]. Of interest, similar to the case with JCV, BKV was unable to replicate in human monocytes isolated from peripheral blood [38].

Another polyomavirus, hamster polyomavirus, has also been shown to infect lymphocytes. In fact, hamster polyomavirus induces lymphomas and leukemia in newborn hamsters [39, 40]. Moreover, large amounts of extrachromosomal viral genomes are present in the lymphoma cells [41, 42]. These observations pose interesting questions with respect to the oncogenic potential of JCV.

JCV has been shown to cause neuroectodermal tumors in rodents and nonhuman primates [43–50]. Evidence for involvement of JCV in human brain tumors is certainly not as clear. Although JCV has been detected in PML patients with an astrocytoma [51], glioma [52], and CNS lymphoma [53], numerous studies examining larger numbers of CNS tumors have been unable to detect JCV [54–56]. Nonetheless, the ability of JCV to transform both human and nonhuman cells in vitro is described [57–59]. Moreover, Neel et al. [60] demonstrated that infection of HFGC with JCV produces ploidy and chromosomal damage.

The oncogenic potential of JCV is noteworthy with respect to the background in which PML develops. PML is usually associated with immunocompromised conditions. The majority of PML cases occur in AIDS patients. In fact, ~4% of all AIDS patients will develop this neurodegenerative disease [61]. HIV-1-infected persons are not only prone to developing infectious opportunistic diseases but are also at risk of developing a variety of neoplastic diseases. Among the neoplastic diseases that occur with an increased frequency in HIV-1-infected persons are Kaposi’s sarcoma and non-Hodgkin’s lymphoma. AIDS-associated lymphomas are usually a late manifestation of HIV-1 infection with CD4 T cell counts <200 cells/mm³. It is interesting to note that most of these lymphomas are B cell in origin. The most common types include large cell immunoblastic, small noncleaved cell (Burkitt’s), and large cell cleaved or noncleaved. There are many pathogenetic mechanisms proposed to explain AIDS-associated lymphomas, including EBV infection as well as alterations in protooncogenes and/or tumor suppressor genes. Despite these numerous proposed mechanisms, a significant number of AIDS-associated lymphomas are yet unexplained.

Given the existence of JCV in B cells, the ability of JCV to replicate within and productively infect B cells, and the oncogenic potential of JCV, it is tempting to envision a participatory role for JCV (and/or BKV) in AIDS-associated B cell lymphomas. This is interesting in light of the recent observation that...
JCV participates in the etiology of "rogue" cells, lymphocytes that exhibit chromosomal damage in the absence of any known cause [60]. In fact, JCV DNA and T antigen have been demonstrated in eight AIDS-associated lymphomas (Houff SA, unpublished observations). The relevance of JCV-infected B cells to the development of AIDS-associated lymphomas is complicated by the various other processes that occur during AIDS (e.g., depressed cell-mediated immunity, altered cytokine levels). Nonetheless, the existence of JCV in lymphocytes necessitates further study into the potential association of JCV with a disease other than PML.

Summary

Much has been learned about the cellular and molecular biology of JCV and the pathogenesis of PML since JCV was first cultivated some 25 years ago. Nine years ago, JCV was demonstrated in lymphocytes in patients with PML. Since that report, many studies have now demonstrated the presence of JCV DNA and capsid antigen in mononuclear cells in the bone marrow, CNS, and peripheral blood. Thus, JCV should no longer be classified solely as a neurotropic virus; the numerous studies described here support the hypothesis that JCV is lymphotropic as well. The precise role lymphocytes play in the life cycle of this papovavirus and the pathogenesis of PML and potentially other human diseases is only beginning to be understood.

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References