Published in final edited form as:
Virology. 2009 February 20; 384(2): 266–273. doi:10.1016/j.virol.2008.09.027.

The Role of Polyomaviruses in Human Disease

Mengxi Jiang[1], **Johanna R. Abend**[1], **Silas F. Johnson**, and **Michael J. Imperiale**[*]
Department of Microbiology and Immunology, and Comprehensive Cancer Center, University of Michigan Medical School, Ann Arbor, MI 48109, USA

Abstract

The human polyomaviruses, BK virus and JC virus, have long been associated with serious diseases including polyomavirus nephropathy and progressive multifocal leukoencephalopathy. Both viruses establish ubiquitous, persistent infections in healthy individuals. Reactivation can occur when the immune system is impaired, leading to disease progression. Recently, the human polyomavirus family has expanded with the identification of three new viruses (KI, WU and Merkel cell polyomavirus), all of which may prove to be involved in human disease. This review describes the general aspects of human polyomavirus infections and pathogenicity. Current topics of investigation and future directions in the field are also discussed.

Keywords

polyomavirus; JCV; BKV; PML; polyomavirus nephropathy; KI; WU; MCV

Discovery of Human Polyomaviruses

The first human polyomaviruses, BK virus (BKV) and JC virus (JCV), were coincidently isolated in 1971 by two independent groups, BKV from the urine of a renal transplant patient who suffered from ureteral stenosis (Gardner et al., 1971) and JCV from the brain tissue of a patient with Hodgkin's lymphoma who developed progressive multifocal leukoencephalopathy (PML) (Padgett et al., 1971). Nearly four decades passed before DNA sequences representing three new members of the human polyomavirus family were discovered. Viral genomes cloned from these sequences have been designated KI polyomavirus (KI), WU polyomavirus (WU), and Merkel cell polyomavirus (MCV). KI and WU were identified from large-scale high-throughput screens of respiratory secretions from patients with respiratory tract infections (Allander et al., 2007; Gaynor et al., 2007), and MCV was identified in Merkel cell carcinomas (MCC) using digital transcriptome subtraction (Feng et al., 2008). The human polyomaviruses have a tradition of nomenclature based on the origin of the isolate: BKV and JCV take their names from the initials of the patients from whom they were isolated, while KI and WU are named after the institutions where they were discovered. Only MCV departs from this convention as it is named after the type of tumor from which it was identified. This review will focus on BKV and JCV, whose roles as human pathogens are best understood.

*Corresponding author: Mailing address: University of Michigan Medical School, 1150 West Medical Center Drive, 5724 Medical Science II, Ann Arbor, MI 48109-5620, Phone: (734) 763-9162, Fax: (734) 615-6560, Email: imperial@umich.edu.
[1]These authors contributed equally.

General Aspects of Polyomavirus Infection

The human polyomaviruses, as with all polyomaviruses, are composed of small, non-enveloped, icosahedral virions with a supercoiled double-stranded DNA genome (Imperiale and Major, 2007). The virion consists of 72 pentamers of the major capsid protein VP1, with each pentamer associated with a single copy of the minor capsid protein VP2 or VP3 (Liddington et al., 1991; Stehle et al., 1996). The viral genome is associated with cellular histones to form a so-called minichromosome, the structure of which is similar to host chromatin (Meneguzzi et al., 1978; Muller et al., 1978). Polyomaviruses are known to have very restricted host ranges; accordingly, BKV and JCV are only known to productively infect and cause disease in humans.

The genomes of BKV and JCV are divided into three regions: the early coding region, which encodes the large tumor antigen (TAg) and small tumor antigen (tAg); the late coding region, which encodes the viral capsid proteins VP1, VP2 and VP3, and the nonstructural agnoprotein; and the non-coding control region (NCCR), which contains the viral promoters and origin of replication. These viruses also encode auxiliary T antigens that are derived from alternative splicing of the TAg transcript (Bollag et al., 1989; Trowbridge and Frisque, 1995). KI and WU share the most significant homology with BKV and JCV in regards to genome organization and amino acid sequence of predicted viral proteins (Allander et al., 2007; Gaynor et al., 2007). MCV on the other hand is most similar to the African green monkey lymphotropic polyomavirus (LPV) (Feng et al., 2008).

Route of Transmission and Seroconversion

The mode of transmission for BKV and JCV is not yet well defined, however, evidence suggesting respiratory transmission is present in the literature. A study of children with respiratory diseases showed that a high percentage of tonsillar tissues contained nonintegrated forms of BKV DNA (Goudsmit et al., 1982). Similarly, the presence of JCV DNA in B cells and stromal cells of the tonsils and oropharynx supports this hypothesis (Monaco et al., 1998a). Seroconversion for both viruses is widespread and occurs in childhood, with BKV seropositivity reaching 90% in children aged 5 to 9 and JCV seropositivity reaching 50 to 60% after the age of 10 (Knowles, 2006). Potential alternative modes of transmission for these viruses include urino-oral, transplancental, and transmission by blood transfusion, semen and organ transplantation (Bofill-Mas et al., 2001; Bofill-Mas et al., 2000; Hirsch and Steiger, 2003).

Adult seroprevalence for BKV and JCV is very high: more than 90% of the adult population is seropositive for BKV (Knowles et al., 2003), while 50 to 80% of adults have antibodies to JCV (Khalili et al., 2007; Knowles, 2006). Interestingly, the antibody titer against BKV decreases as the age increases, while that of JCV remains relatively unchanged (Knowles, 2006; Knowles et al., 2003). In addition, there is a negative association between the seropositivity of BKV and JCV, with BKV seronegative individuals more likely to be JCV seropositive, suggesting that these two viruses may either be transmitted through different mechanisms or that infection with BKV may provide some protective effects against JCV (Knowles et al., 2003; Taguchi et al., 1982).

Dissemination and Persistence

Primary infections with BKV and JCV are typically subclinical or linked to mild respiratory illness (Goudsmit et al., 1981; Goudsmit et al., 1982), and are followed by viral dissemination to the sites of lifelong persistent infection. The major sites of persistence for both BKV and JCV are the cells of the kidney and urinary tract (Chesters et al., 1983; Heritage et al., 1981). BKV DNA has been found in 30 to 50% of normal kidney tissues, with distribution patterns

of small foci throughout the cortex and medulla, and in 40% of ureters (Monini et al., 1995; Nickeleit et al., 2003). In addition, BKV-specific immunostaining analyses identified epithelial cells of the kidney, ureter and bladder as the predominant cell types that are persistently infected (Shinohara et al., 1993). JCV DNA can be detected in approximately 10 to 50% of normal kidney samples, although at lower levels than BKV DNA (Aoki et al., 1999; Chesters et al., 1983; Grinnell et al., 1983). Numerous reports of JCV DNA in lymphocytes argue for the importance of these cells in persistence and dissemination via circulatory routes (Doerries, 2006; Doerries et al., 2003; Doerries et al., 1994; Monaco et al., 1998b; Monaco et al., 1996; Tornatore et al., 1992). It is not known whether the viruses enter a latent state or maintain a low level of viral gene expression and replication at these sites, although intermittent replication must occur as evidenced by periodic excretion of virus in the urine. Approximately 5% of immunocompetent individuals have BKV viruria while 20 to 30% are actively shedding JCV (Doerries, 2001; Knowles, 2001). In addition, asymptomatic viruria has been observed in approximately 3% of pregnant women during the second and third trimesters (Arthur and Shah, 1989; Chang et al., 1996b; Coleman et al., 1980; Markowitz et al., 1991). How the host innate, humoral, and cellular immune responses control these persistent infections remains unknown.

A variety of other cell types have been reported to contain BKV and JCV sequences, and it has been suggested that infection of these cells may be involved in dissemination or persistence. BKV sequences have been detected at a high frequency in urogenital tissues and fluids including cervix, vulva, prostate, and semen, and a relatively lower frequency in brain tissues, consistent with its urotheliotropic nature (Doerries, 2006; Elsner and Dorries, 1992; Martini et al., 2004; Monini et al., 1996; Monini et al., 1995; Pietropaolo et al., 2003). Moreover, BKV DNA has been found in peripheral blood mononuclear cells and spleen (Chatterjee et al., 2000; Dorries et al., 1994; Pietropaolo et al., 2003), suggesting the involvement of the immune system in BKV spread. Additionally, endothelial cells have been shown to support BKV replication *in vitro*, raising the possibility that BKV may cross the endothelial barrier to disseminate from the periphery to its target organs via blood (Hanssen Rinaldo et al., 2005). There are rare reports of JCV sequence detection in various tissues and cells including the liver, lung, spleen, lymph nodes, and colorectal epithelium (Caldarelli-Stefano et al., 1999; Doerries, 2001; Grinnell et al., 1983; Laghi et al., 1999; Newman and Frisque, 1997; Newman and Frisque, 1999). While JCV reactivation leads primarily to infection of the brain, it is unclear whether normal brain tissue harbors the virus (Doerries, 2001). Many researchers have reported the presence (Caldarelli-Stefano et al., 1999; Elsner and Dorries, 1992; Mori et al., 1992) or absence (Chesters et al., 1983; Quinlivan et al., 1992; Stoner et al., 1988) of JCV sequences in the brains of patients without PML. Overall, however, these studies are small with significant variation in the health conditions of the individuals.

Reactivation during Immunosuppression

Human polyomaviruses cause significant disease primarily in individuals that are immunocompromised, allowing reactivation from the persistent subclinical state to a lytic infection resulting in viruria and viremia, potentially leading to severe or fatal diseases (Table 1).

For BKV, reactivation is most common in bone marrow transplant (BMT) and renal transplant patients, where BKV lytic infection results in hemorrhagic cystitis (HC) and polyomavirus nephropathy (PVN), respectively. In addition, reactivation has been observed in individuals with altered immune conditions including other solid organ transplantations, autoimmune diseases such as systemic lupus erythematosus (SLE), and patients with acquired immunodeficiency syndrome (AIDS) (Chang et al., 1996a; Munoz et al., 2005; Sundsfjord et al., 1999). The levels of BKV viruria correlate with the degree of immunosuppression, indicating that viral replication results from the reactivation of a persistent infection rather than

reinfection (Ahsan and Shah, 2006; Doerries, 2001). In patients with SLE, it has also been suggested that BKV infection might initiate autoimmunity by inducing antibodies against DNA and histones (Rekvig et al., 1997). In the context of HIV infection, BKV viruria has been shown to increase concomitantly with a decrease in CD4+ T cell counts (Gluck et al., 1994; Knowles et al., 1999). Although very rare, BKV has also been linked to meningoencephalitis, retinitis, and lung infection in AIDS patients and individuals undergoing immunosuppression (Bratt et al., 1999; Cubukcu-Dimopulo et al., 2000; Vallbracht et al., 1993).

The most common underlying cause of immunosuppression leading to JCV reactivation is AIDS. Reactivation results in the lytic infection of oligodendrocytes in the brain and the development of PML. Other immune-altering conditions in which cases of PML have been reported include lymphoproliferative diseases such as lymphomas and leukemias, myeloproliferative diseases, transplantation, chemotherapy, multiple sclerosis (MS), and inherited immunodeficiences (Berger, 2003; Berger and Concha, 1995; Brooks and Walker, 1984). In contrast to observations with BKV, JCV viruria does not correlate with the degree of immunosuppression (Doerries, 2001), indicating the importance of other factors during reactivation.

Polyomavirus-associated Diseases

BK Virus and Polyomavirus Nephropathy

PVN, the most frequent BKV-associated disease after renal transplantation, is a form of acute interstitial nephritis (Nickeleit and Mihatsch, 2006). BKV viruria and viremia due to reactivation are found in up to 80% of renal transplant patients and 10% of patients progress to PVN, resulting in allograft loss 90% of the time (Binet et al., 1999; Bressollette-Bodin et al., 2005; Egli et al., 2007; Hirsch et al., 2002). PVN is characterized by necrosis of proximal tubules and denudation of the basement membrane as a result of BKV lytic infection in kidney epithelial cells (Nickeleit et al., 2003). Recently, the incidence of PVN has been rising with the introduction of new and more potent immunosuppressive regimens (Binet et al., 1999; Mengel et al., 2003; Nickeleit et al., 2000), indicating a relationship between BKV reactivation and the disruption of the immune system. The current standard of diagnosis of PVN includes analysis of renal biopsies using histopathology or immunohistochemistry, either to detect cytopathic changes as a result of injury or lysis of renal tubular epithelial cells, or to detect viral gene expression. In addition, urine cytology is used to detect decoy cells, which are epithelial cells with intranuclear viral inclusion bodies, and PCR to detect viral genomes and quantify viral load in blood or urine samples (Drachenberg et al., 2005; Vats et al., 2006). PCR and urine cytology may be more useful for detecting the early stages of reactivation and PVN (Hirsch et al., 2002; Ramos et al., 2002b), thus allowing for faster diagnosis and intervention, with a consequent increase in graft survival (Drachenberg et al., 2004).

There is no single risk factor associated with the development of PVN. Instead it is thought that what determines susceptibility to BKV reactivation is a combination of contributing factors from the virus, patient, and graft. The overall degree of immunosuppression, and not the particular immunosuppressive drugs employed, is suggested to be the major risk factor for PVN (Bonvoisin et al., 2008). Impairment of the immune system alone, however, is not sufficient for the development of PVN, as the disease manifestation is relatively uncommon in nonrenal solid organ transplant and other immunosuppressed patients (Hirsch, 2005; Pavlakis et al., 2006). Other suggested risk factors include donor seropositivity, specific HLA locus or HLA mismatches, anti-rejection treatment, older age, and male gender (Bohl et al., 2005; Hirsch et al., 2002; Ramos et al., 2002a; Ramos et al., 2002b).

The immune response to BKV during PVN is an active area of investigation. A critical question that arises is what facet of the immune response is important for maintaining control over

infection. The humoral response does not appear to be sufficient to restrict BKV infection, as it is reported that approximately 70% of patients are seropositive for BKV before renal transplantation (Hirsch et al., 2002) and that individuals with detectable anti-BKV antibodies still progress to PVN (Comoli et al., 2006). Instead, it seems that antibodies are more indicative of the viral load in a patient rather than protection against BKV infection, as high levels of antibodies in PVN patients correlate with high levels of viremia and low $CD8^+$ T cell responses (Chen et al., 2006). The cell-mediated immune response may be more relevant to disease development: low levels of BKV-specific IFN-γ-producing T cells correlate with progression to PVN, while reconstitution of these cells correlates with resolution of PVN (Binggeli et al., 2007; Chen et al., 2006; Prosser et al., 2008). Moreover, *in vitro* studies have demonstrated that IFN-γ strongly inhibits BKV replication in kidney epithelial cells (Abend et al., 2007). Therefore, it is suspected that the effector functions and cytokines produced by T cells may be a crucial means to control BKV replication and reactivation.

At this time, effective and specific anti-viral treatments for BKV do not exist: the most common initial intervention is to decrease immunosuppression to allow the host immune system to regain control over the infection. This, however, leaves the patients at risk for acute graft rejection and is not effective in all patients. Cidofovir is an antiviral nucleoside analogue which is known to inhibit BKV DNA replication (Bernhoff et al., 2008), but can be nephrotoxic at high doses (Blanckaert and De Vriese, 2006). There are some recent indications, however, that when this drug is used at low doses and in combination with a reduction in immunosuppression, it may be effective against BKV reactivation without causing significant nephrotoxicity (Bjorang et al., 2002; Kadambi et al., 2003; Kuypers et al., 2005). In addition, there has been some limited success with leflunomide, an immunosuppressive drug (Faguer et al., 2007; Josephson et al., 2006; Williams et al., 2005). Other antiviral treatments that have been used in clinical trials include intravenous immunoglobulin (IVIG) and fluoroquinolone antibiotics (Bonvoisin et al., 2008; Rinaldo and Hirsch, 2007; Sener et al., 2006; Sessa et al., 2008). However, more systematic studies are warranted to evaluate the efficacies of these treatments. Finally, retransplantation following nephrectomy, to rapidly clear the viral source, is another therapeutic approach (Funk et al., 2006; Poduval et al., 2002).

BK Virus and Hemorrhagic Cystitis

HC is a serious BKV-associated complication characterized by dysuria and varying degrees of hematuria that affects up to 10% of BMT patients (Dropulic and Jones, 2008). The first association of BKV reactivation with HC was reported in the late 1970s and was further established in the 1980s (Arthur et al., 1985; Hashida et al., 1976; Mininberg et al., 1982). HC is likely due to viral reactivation in the uroepithelium, as BKV virions can be detected in exfoliated epithelial cells (Fogazzi et al., 2001; Hiraoka et al., 1991). Moreover, the level of viruria correlates with the development of HC (Arthur et al., 1986; Bogdanovic et al., 2004). Typically, BKV-associated HC occurs more than 10 days post-transplant (late-onset) and requires medical attention: while not usually life-threatening, HC is associated with significant morbidity (Apperley et al., 1987; Azzi et al., 1999; Bedi et al., 1995; Egli et al., 2007). Urine cytology and PCR detection of viral DNA are the most commonly used methods for diagnosis of BKV-associated HC (Dropulic and Jones, 2008). As with PVN, antivirals such as cidofovir and fluoroquinolone antibiotics are currently being tested for their effectiveness in treating BKV-associated HC (Held et al., 2000; Leung et al., 2005; Savona et al., 2007).

JC Virus and Progressive Multifocal Leukoencephalopathy

PML was originally described in 1958 as a demyelinating disease of the central nervous system (Astrom et al., 1958), and later viral particles were detected by electron microscopy in the brains of patients with PML (Silverman and Rubinstein, 1965; Zurhein and Chou, 1965). It became apparent that JCV infection is the cause of PML, as essentially all brain and

cerebrospinal fluid (CSF) samples from these affected patients have detectable levels of JCV DNA and proteins (Gibson et al., 1993; Grinnell et al., 1983; Stoner et al., 1986; Taoufik et al., 1998). Initially, PML was a fairly rare malady associated with immunosuppressed patients, primarily those with lymphomas and leukemias (Johnson, 1982; Walker, 1985). With the rise of the AIDS epidemic, however, JCV infections resulting in PML have risen dramatically. The majority (55 to 85%) of PML cases occur in patients with AIDS (Berger and Nath, 2001; Major et al., 1992), with only sporadic cases of PML developing without an underlying immune disorder (Brooks and Walker, 1984; Safak and Khalili, 2003). As such, PML is now considered an AIDS-defining illness (Stoner et al., 1986). Approximately 6% of HIV cases have JCV replication in the kidneys and approximately 5% of individuals with HIV develop PML (Berger, 2003; Berger and Concha, 1995; Boldorini et al., 2003; Stoner et al., 1986).

Clinically, PML is characterized by impaired speech and vision, dementia or confusion, and varying degrees of paralysis or akinesia, in conjunction with an immunocompromised state and a lack of increase in intracranial pressure (Berger and Concha, 1995; Brooks and Walker, 1984). The subsequent disease progression is rapid, with clinical symptoms intensifying and death of the patient within 3 to 6 months (Berger et al., 1998). At the cellular level, PML is a cytolytic infection of oligodendrocytes, the myelin producing cells of the brain. Infection results in cell death and development of lesions in the cerebrum, cerebellum and brain stem, particularly along the junction of the gray and white matter (Berger and Major, 1999; Whiteman et al., 1993). Neurons are not affected and astrocytes can be infected nonpermissively, only expressing TAg and not progressing to cell lysis (Aksamit, 1995; Berger and Concha, 1995; Johnson, 1982). In addition, JCV sequences have been detected in other cells within the brain including B cells and mononuclear cells (Hou et al., 2006; Houff et al., 1988; Major et al., 1990; von Einsiedel et al., 2004). Other characteristics of PML include enlarged JCV TAg-expressing oligodendrocytes with nuclear inclusion bodies and crystalline arrays of viral particles, an increasing presence of macrophages, and enlarged, so-called bizarre astrocytes with lobulated, hyperchromatic nuclei (Berger and Nath, 2001; Major et al., 1992). The widespread distribution of brain lesions and the high frequency of JCV-positive peripheral blood cells suggest that lymphocytes can serve as a reservoir and dissemination vehicle (Jensen and Major, 1999; Koralnik et al., 1999b; Major et al., 1992). It is not clear if JCV infection of the brain is a result of *de novo* invasion of the virus or reactivation of a persistent infection (Doerries, 2006; White et al., 1992). PML patients, however, do not have enhanced viruria and renal infection as compared to healthy controls (Arthur and Shah, 1989; Doerries, 2001; Koralnik et al., 1999a).

The underlying cause for the association between JCV-associated PML and HIV/AIDS is not fully understood. Several hypotheses may explain the link between these two virus-associated diseases (Berger, 2003; Berger et al., 2001; Khalili et al., 2006; Seth et al., 2003). First, HIV establishes a state of profound immunosuppression within the host, and specifically, a decrease in JCV-specific $CD4^+$ T cells as a result of HIV infection could allow uncontested replication of JCV. More directly, HIV infection may result in breakdown of the blood-brain barrier, allowing entry of JCV-harboring B cells into the brain. Furthermore, production of certain cytokines in response to HIV infection may initiate signaling within the cell that results in activation of the JCV promoter. Finally, there is some evidence that the HIV Tat protein is able to act on JCV promoters *in vitro* and promote gene expression (Chowdhury et al., 1992; Tada et al., 1991). In support of this observation, HIV Tat and JCV VP1 expression have been detected in the same areas of the brain that are affected by PML (Del Valle et al., 2000).

The cell-mediated immune response, in particular T cells, appears to be very important for controlling JCV infections. Studies have shown that patients with higher levels of JCV-specific $CD4^+$ and $CD8^+$ T cells have prolonged survival (Berger et al., 1998; Gasnault et al., 2003; Koralnik, 2006). Anti-JCV antibody levels do not change during progression of PML and are

not detected in the CSF, arguing against the involvement of the humoral immune response. Early detection and various therapeutic interventions, including chemotherapy, nucleoside analogs, receptor blockers, and interferon-alpha, have not been effective at increasing survival time (Roskopf et al., 2006). Highly active antiretroviral therapy (HAART), however, has improved the survival of patients to approximately 10.5 months post-onset of clinical symptoms (Cinque et al., 2001; Clifford et al., 1999; De Luca et al., 2000).

JC Virus and Multiple Sclerosis

While MS and PML are both diseases resulting in demyelinated lesions of the brain, they are distinguished by the morphologically-distinct bizarre astrocytes, inclusion bodies within the nuclei of oligodendrocytes, and the lack of inflammatory inflitrates, which are characteristic of PML (Khalili et al., 2007). Still, the similarities between these conditions have prompted an investigation of the association of MS with JCV reactivation and PML. There are conflicting reports of JCV DNA and viremia in patients with MS: several studies report a lack of evidence for JCV infection in MS patients (Bogdanovic et al., 1998; Buckle et al., 1992), while others have found JCV DNA sequences in CSF of some MS patients but not in healthy controls (Ferrante et al., 1998; Koralnik et al., 1999a).

Recently, there have been two cases of PML in MS patients treated in the same clinical trial with a combination therapy of natalizumab (Tysabri), an $\alpha_4\beta_1$ integrin inhibitor that prevents T cell trafficking into the brain, and interferon-β-1A (Avonex) (Kleinschmidt-DeMasters and Tyler, 2005; Langer-Gould et al., 2005). A third case of PML was reported in a patient with Crohn's disease who was also treated with natalizumab (Van Assche et al., 2005). These results suggest that restricting T cell entry into the brain allows reactivation of JCV and development of PML. Further examination of patients undergoing therapy with natalizumab indicated no clear association between PML and treatment: out of 3,417 patients treated with natalizumab, only 44 were suspected of having PML and none of these cases were confirmed (Yousry et al., 2006).

Human Polyomaviruses and Cancer

There is no clear association between BKV and JCV and the development of tumors. Various reports have indicated the presence or absence of viral genomic sequences in multiple human cancers. It has been suggested that that BKV is associated with brain tumors, adenocarcinomas, prostate cancers, and bladder carcinomas, and JCV is associated with mesotheliomas, brain tumors, osteosarcomas, and lymphomas. For a more detailed discussion about the association of human polyomaviruses with cancer, refer to the following reviews (Barbanti-Brodano et al., 2006; Khalili et al., 2006; Lee and Langhoff, 2006) and this issue of Virology.

KI, WU, MCV, and Human Disease

Since KI and WU were first identified, viral sequences have been confirmed in respiratory specimens worldwide (Abed et al., 2007; Abedi Kiasari et al., 2008; Bialasiewicz et al., 2008; Bialasiewicz et al., 2007; Han et al., 2007; Le et al., 2007; Lin et al., 2008; Neske et al., 2008; Norja et al., 2007; Payungporn et al., 2008), suggesting both viruses are widespread among human populations. Furthermore, available data support a model in which primary infection with KI or WU occurs during childhood (Abedi Kiasari et al., 2008; Bialasiewicz et al., 2007; Gaynor et al., 2007). Despite their clear presence in specimens of patients with respiratory illnesses, the pathogenicity of KI and WU remains speculative. The proposed association of KI and WU with respiratory disease is tenuous because the majority of studies to date have not included specimens from asymptomatic patients. In the three studies that included these control groups, viral sequences were detected at similar frequencies in asymptomatic patients (Abed et al., 2007; Han et al., 2007; Norja et al., 2007). The link between KI and WU infection and respiratory disease is further complicated by the high rates of co-

infection with other respiratory viruses that were observed in these studies (Abedi Kiasari et al., 2008; Allander et al., 2007; Bialasiewicz et al., 2008; Gaynor et al., 2007; Han et al., 2007; Le et al., 2007; Neske et al., 2008). Despite the lack of evidence for KI and WU causing disease, more research is warranted to investigate this possibility, especially considering their similarities to BKV and JCV in nucleotide sequence and potential route of infection.

MCV, the most recently discovered human polyomavirus, has been implicated in the etiology of MCC (Garneski et al., 2008a; zur Hausen, 2008), a rare but aggressive form of skin cancer. Feng *et al.* (2008) identified sequences corresponding to MCV in 8 of 10 MCC tumors, as compared to 5 of 59 control tissues. Viral DNA in 6 of the 8 MCC positive tumors showed a clonal integration pattern. One tumor had similar primary and metastatic integration patterns, suggesting viral integration preceded metastasis. Interestingly, the integrated form of MCV in these tumors is predicted to encode a truncated TAg due to mutations within the second exon of the TAg gene. This truncation would result in the loss of TAg domains required for viral DNA replication and p53 binding but does not affect domains required for inducing cell-cycle progression, suggesting this predicted protein may retain its transformation capability. Subsequent studies have confirmed the presence of MCV sequences in MCC tumors at similar frequencies as the original study (Becker et al., 2008; Foulongne et al., 2008; Garneski et al., 2008b; Kassem et al., 2008). Despite the presence of MCV in significant numbers of Merkel cell tumors, the involvement of this virus in the development of MCC is still uncertain. More studies are required to determine if MCV integration or potential expression of oncogenic viral T antigens contributes to MCC.

Unanswered Questions in Human Polyomavirus Pathogenesis

While we understand much of the molecular biology of human polyomaviruses, basic questions about the viruses themselves and their interactions with the host remain unanswered. First, it is unclear how the viruses spread throughout the population. While it is apparent that BKV and JCV are shed in urine, their detection in tonsillar lymphocytes could be indicative of transmission via the respiratory route. In addition, it is curious that children seroconvert against BKV at an earlier age than against JCV. One of the most important questions is how the viruses persist in healthy individuals. The answer to this question will require more information on the biology of BKV and JCV in the urinary tract as well as a better understanding of the immune components responsible for controlling viral replication. It is not known whether the viruses undergo some low level of ongoing replication, as evidenced by periodic excretion into the urine, or establish a true latent state. It will also be important to determine whether the cells in which BKV and JCV persist are the same as or different from those in which they replicate to cause disease. To pursue studies of the immune responses to these viruses, researchers may have to rely on an animal model using mouse polyomavirus, although the genetic structure of this virus differs significantly from that of the human viruses in that it encodes a different cadre of T antigens. Lastly, the changes in the host that lead to reactivation must be uncovered in more detail. Clearly immunosuppression plays a major role in reactivation, but not all AIDS patients present with PML and not all transplant patients present with PVN, despite being on the same immunosuppressive regimen. The available evidence suggests that these differences are not due to genetic variation in the viruses themselves. Thus, one must invoke polymorphisms in the human population that affect tropism or perhaps the immune response. Rapid advances in genetics may allow the definition of host gene(s) that determine susceptibility to BKV and JCV reactivation.

For the newly discovered polyomaviruses, some very basic questions must be answered. First and foremost, can infectious MCV, WU, and KI particles be isolated and grown in the laboratory? An experimental system for the propagation of these viruses will be essential to understand their biology. It will also be important to determine if these viruses persist in the

urinary tract like JCV and BKV, or if they are only associated with acute infections or cancers. Furthermore, routes of transmission and epidemiology of KI, WU, and MCV will need to be determined. For MCV, it will be interesting to know if there is selection in MCC for variants that express truncated forms of TAg, and if there is anything unique about Merkel cells that makes them susceptible to oncogenesis by this virus. A related question in the polyomavirus field is whether SV40 is a human pathogen. This question is highly controversial and there are contradictory reports in the literature, with some groups finding viral sequences in various human tumors while other groups failed to detect sequences in the same type of tumor (Garcea and Imperiale, 2003). To date, there is no good serological evidence for SV40 in humans (Carter et al., 2003; Shah et al., 2004) although this does not prove that SV40 is not a human pathogen (Vilchez and Butel, 2004). This long-standing controversy needs resolution since a large number of people were exposed to SV40 in contaminated poliovirus vaccines, and it remains possible that the virus could spread from human to human (Stratton et al., 2002). The recent discoveries of new human polyomaviruses certainly raises the question of whether there are additional viruses in the population and has rekindled interest in previously-identified viruses. For example, there is serologic evidence for LPV infection of humans (Brade et al., 1981; Viscidi and Clayman, 2006; R. Garcea, personal communication). Although current virus discovery attempts are mainly aimed at isolating pathogens from sick individuals, it is possible that there are viruses that are not associated with disease but simply persist and spread without clinical symptoms.

Given the increasing incidence of polyomavirus-associated diseases, particularly the severe diseases in immunocompromised individuals, there is a dire need for more effective and specific antivirals. Cidofovir shows some efficacy but can be nephrotoxic, limiting its utility, especially in renal transplant patients. Candidate targets include small molecules that interfere with TAg function or virion assembly, which could be identified using high-throughput screens. One must also consider whether vaccine development is plausible; the success of the human papillomavirus vaccines, along with the fact that polyomavirus virus-like particles are easily produced, is supportive of the possibility of vaccination.

For many years, much effort was focused on SV40 as a model system for understanding basic eukaryotic processes such as transcription, DNA replication, and oncogenic transformation, while studies of the human polyomaviruses and their roles as human pathogens took a back seat. Since polyomaviruses are highly adapted to their own hosts, each virus must be studied and understood as individual entities. Future studies hold great promise for the ability to detect and combat these important and ubiquitous viruses.

Acknowledgements

We thank Joan Christensen for critical review of the manuscript. This work was supported by AI060584 and CA118970 awarded to M.J.I. from the NIH. M.J. was supported by American Heart Association Postdoctoral Fellowship 0825806G. J.R.A. was supported by the F.G. Novy Fellowship. S.F.J. was supported by NCI Training Grant T32-CA009676.

References

Abed Y, Wang D, Boivin G. WU polyomavirus in children, Canada. Emerg Infect Dis 2007;13:1939–1941. [PubMed: 18258053]

Abedi Kiasari B, Vallely PJ, Corless CE, Al-Hammadi M, Klapper PE. Age-related pattern of KI and WU polyomavirus infection. J Clin Virol 2008;43:123–125. [PubMed: 18573691]

Abend JR, Low JA, Imperiale MJ. Inhibitory effect of gamma interferon on BK virus gene expression and replication. J Virol 2007;81:272–279. [PubMed: 17035315]

Ahsan N, Shah KV. Polyomaviruses and human diseases. Adv Exp Med Biol 2006;577:1–18. [PubMed: 16626024]

Aksamit AJ Jr. Progressive multifocal leukoencephalopathy: a review of the pathology and pathogenesis. Microsc Res Tech 1995;32:302–311. [PubMed: 8573780]

Allander T, Andreasson K, Gupta S, Bjerkner A, Bogdanovic G, Persson MA, Dalianis T, Ramqvist T, Andersson B. Identification of a third human polyomavirus. J Virol 2007;81:4130–4136. [PubMed: 17287263]

Aoki N, Kitamura T, Tominaga T, Fukumori N, Sakamoto Y, Kato K, Mori M. Immunohistochemical detection of JC virus in nontumorous renal tissue of a patient with renal cancer but without progressive multifocal leukoencephalopathy. J Clin Microbiol 1999;37:1165–1167. [PubMed: 10074543]

Apperley JF, Rice SJ, Bishop JA, Chia YC, Krausz T, Gardner SD, Goldman JM. Late-onset hemorrhagic cystitis associated with urinary excretion of polyomaviruses after bone marrow transplantation. Transplantation 1987;43:108–112. [PubMed: 3026070]

Arthur RR, Beckmann AM, Li CC, Saral R, Shah KV. Direct detection of the human papovavirus BK in urine of bone marrow transplant recipients: comparison of DNA hybridization with ELISA. J Med Virol 1985;16:29–36. [PubMed: 2995566]

Arthur RR, Shah KV. The occurrence and significance of papovaviruses BK and JC in the urine. Prog Med Virol 1989;36:42–61. [PubMed: 2555837]

Arthur RR, Shah KV, Baust SJ, Santos GW, Saral R. Association of BK viruria with hemorrhagic cystitis in recipients of bone marrow transplants. N Engl J Med 1986;315:230–234. [PubMed: 3014334]

Astrom KE, Mancall EL, Richardson EP Jr. Progressive multifocal leukoencephalopathy; a hitherto unrecognized complication of chronic lymphatic leukaemia and Hodgkin's disease. Brain 1958;81:93–111. [PubMed: 13523006]

Azzi A, Cesaro S, Laszlo D, Zakrzewska K, Ciappi S, De Santis R, Fanci R, Pesavento G, Calore E, Bosi A. Human polyomavirus BK (BKV) load and haemorrhagic cystitis in bone marrow transplantation patients. J Clin Virol 1999;14:79–86. [PubMed: 10588450]

Barbanti-Brodano G, Sabbioni S, Martini F, Negrini M, Corallini A, Tognon M. BK virus, JC virus and Simian Virus 40 infection in humans, and association with human tumors. Adv Exp Med Biol 2006;577:319–341. [PubMed: 16626046]

Becker JC, Houben R, Ugurel S, Trefzer U, Pfohler C, Schrama D. MC Polyomavirus Is Frequently Present in Merkel Cell Carcinoma of European Patients. J Invest Dermatol. 2008

Bedi A, Miller CB, Hanson JL, Goodman S, Ambinder RF, Charache P, Arthur RR, Jones RJ. Association of BK virus with failure of prophylaxis against hemorrhagic cystitis following bone marrow transplantation. J Clin Oncol 1995;13:1103–1109. [PubMed: 7738616]

Berger JR. Progressive multifocal leukoencephalopathy in acquired immunodeficiency syndrome: explaining the high incidence and disproportionate frequency of the illness relative to other immunosuppressive conditions. J Neurovirol 2003;9:38–41. [PubMed: 12709870]

Berger JR, Chauhan A, Galey D, Nath A. Epidemiological evidence and molecular basis of interactions between HIV and JC virus. J Neurovirol 2001;7:329–338. [PubMed: 11517412]

Berger JR, Concha M. Progressive multifocal leukoencephalopathy: the evolution of a disease once considered rare. J Neurovirol 1995;1:5–18. [PubMed: 9222338]

Berger JR, Levy RM, Flomenhoft D, Dobbs M. Predictive factors for prolonged survival in acquired immunodeficiency syndrome-associated progressive multifocal leukoencephalopathy. Ann Neurol 1998;44:341–349. [PubMed: 9749600]

Berger JR, Major EO. Progressive multifocal leukoencephalopathy. Semin Neurol 1999;19:193–200. [PubMed: 10718540]

Berger, JR.; Nath, A. Clinical progressive multifocal leukoencephalopathy: diagnosis and treatment. In: Khalili, K.; Stoner, GL., editors. Human polyomaviruses: molecular and clinical perspectives. Wiley-Liss; New York: 2001. p. 237-256.

Bernhoff E, Gutteberg TJ, Sandvik K, Hirsch HH, Rinaldo CH. Cidofovir inhibits polyomavirus BK replication in human renal tubular cells downstream of viral early gene expression. Am J Transplant 2008;8:1413–1422. [PubMed: 18510636]

Bialasiewicz S, Whiley DM, Lambert SB, Jacob K, Bletchly C, Wang D, Nissen MD, Sloots TP. Presence of the newly discovered human polyomaviruses KI and WU in Australian patients with acute respiratory tract infection. J Clin Virol 2008;41:63–68. [PubMed: 18083616]

Bialasiewicz S, Whiley DM, Lambert SB, Wang D, Nissen MD, Sloots TP. A newly reported human polyomavirus, KI virus, is present in the respiratory tract of Australian children. J Clin Virol 2007;40:15–18. [PubMed: 17706457]

Binet I, Nickeleit V, Hirsch HH, Prince O, Dalquen P, Gudat F, Mihatsch MJ, Thiel G. Polyomavirus disease under new immunosuppressive drugs: a cause of renal graft dysfunction and graft loss. Transplantation 1999;67:918–922. [PubMed: 10199744]

Binggeli S, Egli A, Schaub S, Binet I, Mayr M, Steiger J, Hirsch HH. Polyomavirus BK-specific cellular immune response to VP1 and large T-antigen in kidney transplant recipients. Am J Transplant 2007;7:1131–1139. [PubMed: 17359507]

Bjorang O, Tveitan H, Midtvedt K, Broch LU, Scott H, Andresen PA. Treatment of polyomavirus infection with cidofovir in a renal-transplant recipient. Nephrol Dial Transplant 2002;17:2023–2025. [PubMed: 12401867]

Blanckaert K, De Vriese AS. Current recommendations for diagnosis and management of polyoma BK virus nephropathy in renal transplant recipients. Nephrol Dial Transplant 2006;21:3364–3367. [PubMed: 16998219]

Bofill-Mas S, Formiga-Cruz M, Clemente-Casares P, Calafell F, Girones R. Potential transmission of human polyomaviruses through the gastrointestinal tract after exposure to virions or viral DNA. J Virol 2001;75:10290–10299. [PubMed: 11581397]

Bofill-Mas S, Pina S, Girones R. Documenting the epidemiologic patterns of polyomaviruses in human populations by studying their presence in urban sewage. Appl Environ Microbiol 2000;66:238–245. [PubMed: 10618230]

Bogdanovic G, Priftakis P, Giraud G, Kuzniar M, Ferraldeschi R, Kokhaei P, Mellstedt H, Remberger M, Ljungman P, Winiarski J, Dalianis T. Association between a high BK virus load in urine samples of patients with graft-versus-host disease and development of hemorrhagic cystitis after hematopoietic stem cell transplantation. J Clin Microbiol 2004;42:5394–5396. [PubMed: 15528753]

Bogdanovic G, Priftakis P, Hammarin AL, Soderstrom M, Samuelson A, Lewensohn-Fuchs I, Dalianis T. Detection of JC virus in cerebrospinal fluid (CSF) samples from patients with progressive multifocal leukoencephalopathy but not in CSF samples from patients with herpes simplex encephalitis, enteroviral meningitis, or multiple sclerosis. J Clin Microbiol 1998;36:1137–1138. [PubMed: 9542955]

Bohl DL, Storch GA, Ryschkewitsch C, Gaudreault-Keener M, Schnitzler MA, Major EO, Brennan DC. Donor origin of BK virus in renal transplantation and role of HLA C7 in susceptibility to sustained BK viremia. Am J Transplant 2005;5:2213–2221. [PubMed: 16095500]

Boldorini R, Omodeo-Zorini E, Nebuloni M, Benigni E, Vago L, Ferri A, Monga G. Lytic JC virus infection in the kidneys of AIDS subjects. Mod Pathol 2003;16:35–42. [PubMed: 12527711]

Bollag B, Chuke WF, Frisque RJ. Hybrid genomes of the polyomaviruses JC virus, BK virus, and simian virus 40: identification of sequences important for efficient transformation. J Virol 1989;63:863–872. [PubMed: 2536108]

Bonvoisin C, Weekers L, Xhignesse P, Grosch S, Milicevic M, Krzesinski JM. Polyomavirus in renal transplantation: a hot problem. Transplantation 2008;85:S42–48. [PubMed: 18401263]

Brade L, Muller-Lantzsch N, zur Hausen H. B-lymphotropic papovavirus and possibility of infections in humans. J Med Virol 1981;6:301–308. [PubMed: 7017066]

Bratt G, Hammarin AL, Grandien M, Hedquist BG, Nennesmo I, Sundelin B, Seregard S. BK virus as the cause of meningoencephalitis, retinitis and nephritis in a patient with AIDS. Aids 1999;13:1071–1075. [PubMed: 10397537]

Bressollette-Bodin C, Coste-Burel M, Hourmant M, Sebille V, Andre-Garnier E, Imbert-Marcille BM. A prospective longitudinal study of BK virus infection in 104 renal transplant recipients. Am J Transplant 2005;5:1926–1933. [PubMed: 15996241]

Brooks BR, Walker DL. Progressive multifocal leukoencephalopathy. Neurol Clin 1984;2:299–313. [PubMed: 6503939]

Buckle GJ, Godec MS, Rubi JU, Tornatore C, Major EO, Gibbs CJ Jr, Gajdusek DC, Asher DM. Lack of JC viral genomic sequences in multiple sclerosis brain tissue by polymerase chain reaction. Ann Neurol 1992;32:829–831. [PubMed: 1335225]

Caldarelli-Stefano R, Vago L, Omodeo-Zorini E, Mediati M, Losciale L, Nebuloni M, Costanzi G, Ferrante P. Detection and typing of JC virus in autopsy brains and extraneural organs of AIDS patients and non-immunocompromised individuals. J Neurovirol 1999;5:125–133. [PubMed: 10321976]

Carter JJ, Madeleine MM, Wipf GC, Garcea RL, Pipkin PA, Minor PD, Galloway DA. Lack of serologic evidence for prevalent simian virus 40 infection in humans. J Natl Cancer Inst 2003;95:1522–1530. [PubMed: 14559874]

Chang D, Tsai RT, Wang M, Ou WC. Different genotypes of human polyomaviruses found in patients with autoimmune diseases in Taiwan. J Med Virol 1996a;48:204–209. [PubMed: 8835356]

Chang D, Wang M, Ou WC, Lee MS, Ho HN, Tsai RT. Genotypes of human polyomaviruses in urine samples of pregnant women in Taiwan. J Med Virol 1996b;48:95–101. [PubMed: 8825717]

Chatterjee M, Weyandt TB, Frisque RJ. Identification of archetype and rearranged forms of BK virus in leukocytes from healthy individuals. J Med Virol 2000;60:353–362. [PubMed: 10630970]

Chen Y, Trofe J, Gordon J, Du Pasquier RA, Roy-Chaudhury P, Kuroda MJ, Woodle ES, Khalili K, Koralnik IJ. Interplay of cellular and humoral immune responses against BK virus in kidney transplant recipients with polyomavirus nephropathy. J Virol 2006;80:3495–3505. [PubMed: 16537617]

Chesters PM, Heritage J, McCance DJ. Persistence of DNA sequences of BK virus and JC virus in normal human tissues and in diseased tissues. J Infect Dis 1983;147:676–684. [PubMed: 6302172]

Chowdhury M, Taylor JP, Chang CF, Rappaport J, Khalili K. Evidence that a sequence similar to TAR is important for induction of the JC virus late promoter by human immunodeficiency virus type 1 Tat. J Virol 1992;66:7355–7361. [PubMed: 1331525]

Cinque P, Pierotti C, Vigano MG, Bestetti A, Fausti C, Bertelli D, Lazzarin A. The good and evil of HAART in HIV-related progressive multifocal leukoencephalopathy. J Neurovirol 2001;7:358–363. [PubMed: 11517417]

Clifford DB, Yiannoutsos C, Glicksman M, Simpson DM, Singer EJ, Piliero PJ, Marra CM, Francis GS, McArthur JC, Tyler KL, Tselis AC, Hyslop NE. HAART improves prognosis in HIV-associated progressive multifocal leukoencephalopathy. Neurology 1999;52:623–625. [PubMed: 10025799]

Coleman DV, Wolfendale MR, Daniel RA, Dhanjal NK, Gardner SD, Gibson PE, Field AM. A prospective study of human polyomavirus infection in pregnancy. J Infect Dis 1980;142:1–8. [PubMed: 6249869]

Comoli P, Binggeli S, Ginevri F, Hirsch HH. Polyomavirus-associated nephropathy: update on BK virus-specific immunity. Transpl Infect Dis 2006;8:86–94. [PubMed: 16734631]

Cubukcu-Dimopulo O, Greco A, Kumar A, Karluk D, Mittal K, Jagirdar J. BK virus infection in AIDS. Am J Surg Pathol 2000;24:145–149. [PubMed: 10632500]

De Luca A, Giancola ML, Ammassari A, Grisetti S, Paglia MG, Gentile M, Cingolani A, Murri R, Liuzzi G, Monforte AD, Antinori A. The effect of potent antiretroviral therapy and JC virus load in cerebrospinal fluid on clinical outcome of patients with AIDS-associated progressive multifocal leukoencephalopathy. J Infect Dis 2000;182:1077–1083. [PubMed: 10979902]

Del Valle L, Croul S, Morgello S, Amini S, Rappaport J, Khalili K. Detection of HIV-1 Tat and JCV capsid protein, VP1, in AIDS brain with progressive multifocal leukoencephalopathy. J Neurovirol 2000;6:221–228. [PubMed: 10878711]

Doerries, K. Latent and Persistent Polyomavirus Infection. In: Khalili, K.; Stoner, GL., editors. Human Polyomaviruses: Molecular and Clinical Perspectives. Wiley-Liss; New York: 2001. p. 197-235.

Doerries K. Human polyomavirus JC and BK persistent infection. Adv Exp Med Biol 2006;577:102–116. [PubMed: 16626031]

Doerries K, Sbiera S, Drews K, Arendt G, Eggers C, Doerries R. Association of human polyomavirus JC with peripheral blood of immunoimpaired and healthy individuals. J Neurovirol 2003;9:81–87. [PubMed: 12709877]

Doerries K, Vogel E, Gunther S, Czub S. Infection of human polyomaviruses JC and BK in peripheral blood leukocytes from immunocompetent individuals. Virology 1994;198:59–70. [PubMed: 8259683]

Dorries K, Vogel E, Gunther S, Czub S. Infection of human polyomaviruses JC and BK in peripheral blood leukocytes from immunocompetent individuals. Virology 1994;198:59–70. [PubMed: 8259683]

Drachenberg CB, Hirsch HH, Ramos E, Papadimitriou JC. Polyomavirus disease in renal transplantation: review of pathological findings and diagnostic methods. Hum Pathol 2005;36:1245–1255. [PubMed: 16311117]

Drachenberg CB, Papadimitriou JC, Wali R, Nogueira J, Mendley S, Hirsch HH, Cangro CB, Klassen DK, Weir MR, Bartlett ST, Ramos E. Improved outcome of polyoma virus allograft nephropathy with early biopsy. Transplant Proc 2004;36:758–759. [PubMed: 15110653]

Dropulic LK, Jones RJ. Polyomavirus BK infection in blood and marrow transplant recipients. Bone Marrow Transplant 2008;41:11–18. [PubMed: 17952131]

Egli A, Binggeli S, Bodaghi S, Dumoulin A, Funk GA, Khanna N, Leuenberger D, Gosert R, Hirsch HH. Cytomegalovirus and polyomavirus BK posttransplant. Nephrol Dial Transplant 2007;22:viii72–viii82. [PubMed: 17890268]

Elsner C, Dorries K. Evidence of human polyomavirus BK and JC infection in normal brain tissue. Virology 1992;191:72–80. [PubMed: 1329338]

Faguer S, Hirsch HH, Kamar N, Guilbeau-Frugier C, Ribes D, Guitard J, Esposito L, Cointault O, Modesto A, Lavit M, Mengelle C, Rostaing L. Leflunomide treatment for polyomavirus BK-associated nephropathy after kidney transplantation. Transpl Int 2007;20:962–969. [PubMed: 17666021]

Feng H, Shuda M, Chang Y, Moore PS. Clonal integration of a polyomavirus in human Merkel cell carcinoma. Science 2008;319:1096–1100. [PubMed: 18202256]

Ferrante P, Omodeo-Zorini E, Caldarelli-Stefano R, Mediati M, Fainardi E, Granieri E, Caputo D. Detection of JC virus DNA in cerebrospinal fluid from multiple sclerosis patients. Mult Scler 1998;4:49–54. [PubMed: 9599333]

Fogazzi GB, Cantu M, Saglimbeni L. 'Decoy cells' in the urine due to polyomavirus BK infection: easily seen by phase-contrast microscopy. Nephrol Dial Transplant 2001;16:1496–1498. [PubMed: 11427650]

Foulongne V, Kluger N, Dereure O, Brieu N, Guillot B, Segondy M. Merkel Cell Polyomavirus and Merkel Cell Carcinoma, France. Emerg Infect Dis 2008;14:1491–1493. [PubMed: 18760031]

Funk GA, Steiger J, Hirsch HH. Rapid dynamics of polyomavirus type BK in renal transplant recipients. J Infect Dis 2006;193:80–87. [PubMed: 16323135]

Garcea RL, Imperiale MJ. Simian virus 40 infection of humans. J Virol 2003;77:5039–5045. [PubMed: 12692206]

Gardner SD, Field AM, Coleman DV, Hulme B. New human papovavirus (B.K.) isolated from urine after renal transplantation. Lancet 1971;1:1253–1257. [PubMed: 4104714]

Garneski KM, DeCaprio JA, Nghiem P. Does a new polyomavirus contribute to Merkel cell carcinoma? Genome Biol 2008a;9:228. [PubMed: 18598371]

Garneski KM, Warcola AH, Feng Q, Kiviat NB, Leonard JH, Nghiem P. Merkel Cell Polyomavirus Is More Frequently Present in North American than Australian Merkel Cell Carcinoma Tumors. J Invest Dermatol. 2008b

Gasnault J, Kahraman M, de Goer de Herve MG, Durali D, Delfraissy JF, Taoufik Y. Critical role of JC virus-specific CD4 T-cell responses in preventing progressive multifocal leukoencephalopathy. Aids 2003;17:1443–1449. [PubMed: 12824781]

Gaynor AM, Nissen MD, Whiley DM, Mackay IM, Lambert SB, Wu G, Brennan DC, Storch GA, Sloots TP, Wang D. Identification of a novel polyomavirus from patients with acute respiratory tract infections. PLoS Pathog 2007;3:e64. [PubMed: 17480120]

Gibson PE, Knowles WA, Hand JF, Brown DW. Detection of JC virus DNA in the cerebrospinal fluid of patients with progressive multifocal leukoencephalopathy. J Med Virol 1993;39:278–281. [PubMed: 8388025]

Gluck TA, Knowles WA, Johnson MA, Brook MG, Pillay D. BK virus-associated haemorrhagic cystitis in an HIV-infected man. Aids 1994;8:391–392. [PubMed: 8031522]

Goudsmit J, Baak ML, Sleterus KW, Van der Noordaa J. Human papovavirus isolated from urine of a child with acute tonsillitis. Br Med J (Clin Res Ed) 1981;283:1363–1364.

Goudsmit J, Wertheim-van Dillen P, van Strien A, van der Noordaa J. The role of BK virus in acute respiratory tract disease and the presence of BKV DNA in tonsils. J Med Virol 1982;10:91–99. [PubMed: 6292361]

Grinnell BW, Padgett BL, Walker DL. Distribution of nonintegrated DNA from JC papovavirus in organs of patients with progressive multifocal leukoencephalopathy. J Infect Dis 1983;147:669–675. [PubMed: 6302171]

Han TH, Chung JY, Koo JW, Kim SW, Hwang ES. WU polyomavirus in children with acute lower respiratory tract infections, South Korea. Emerg Infect Dis 2007;13:1766–1768. [PubMed: 18217567]

Hanssen Rinaldo C, Hansen H, Traavik T. Human endothelial cells allow passage of an archetypal BK virus (BKV) strain--a tool for cultivation and functional studies of natural BKV strains. Arch Virol 2005;150:1449–1458. [PubMed: 15770354]

Hashida Y, Gaffney PC, Yunis EJ. Acute hemorrhagic cystitis of childhood and papovavirus-like particles. J Pediatr 1976;89:85–87. [PubMed: 932911]

Held TK, Biel SS, Nitsche A, Kurth A, Chen S, Gelderblom HR, Siegert W. Treatment of BK virus-associated hemorrhagic cystitis and simultaneous CMV reactivation with cidofovir. Bone Marrow Transplant 2000;26:347–350. [PubMed: 10967578]

Heritage J, Chesters PM, McCance DJ. The persistence of papovavirus BK DNA sequences in normal human renal tissue. J Med Virol 1981;8:143–150. [PubMed: 6271922]

Hiraoka A, Ishikawa J, Kitayama H, Yamagami T, Teshima H, Nakamura H, Shibata H, Masaoka T, Ishigami S, Taguchi F. Hemorrhagic cystitis after bone marrow transplantation: importance of a thin sectioning technique on urinary sediments for diagnosis. Bone Marrow Transplant 1991;7:107–111. [PubMed: 1646662]

Hirsch HH. BK virus: opportunity makes a pathogen. Clin Infect Dis 2005;41:354–360. [PubMed: 16007533]

Hirsch HH, Knowles W, Dickenmann M, Passweg J, Klimkait T, Mihatsch MJ, Steiger J. Prospective study of polyomavirus type BK replication and nephropathy in renal-transplant recipients. N Engl J Med 2002;347:488–496. [PubMed: 12181403]

Hirsch HH, Steiger J. Polyomavirus BK. Lancet Infect Dis 2003;3:611–623. [PubMed: 14522260]

Hou J, Seth P, Major EO. JC virus can infect human immune and nervous system progenitor cells: implications for pathogenesis. Adv Exp Med Biol 2006;577:266–273. [PubMed: 16626042]

Houff SA, Major EO, Katz DA, Kufta CV, Sever JL, Pittaluga S, Roberts JR, Gitt J, Saini N, Lux W. Involvement of JC virus-infected mononuclear cells from the bone marrow and spleen in the pathogenesis of progressive multifocal leukoencephalopathy. N Engl J Med 1988;318:301–305. [PubMed: 2827029]

Imperiale, MJ.; Major, EO. Polyomaviruses. In: Knipe, DM.; Howley, PM., editors. Fields Virology. Vol. Fifth. Vol. 2. Lippincott Williams & Wilkins; Philadelphia, PA: 2007. p. 2263-2298.2 vols

Jensen PN, Major EO. Viral variant nucleotide sequences help expose leukocytic positioning in the JC virus pathway to the CNS. J Leukoc Biol 1999;65:428–438. [PubMed: 10204570]

Johnson, R. Progressive multifocal leukoencephalopathy. In: Johnson, R., editor. Viral infections of the nervous system. Raven Press; New York: 1982. p. 255-263.

Josephson MA, Gillen D, Javaid B, Kadambi P, Meehan S, Foster P, Harland R, Thistlethwaite RJ, Garfinkel M, Atwood W, Jordan J, Sadhu M, Millis MJ, Williams J. Treatment of renal allograft polyoma BK virus infection with leflunomide. Transplantation 2006;81:704–710. [PubMed: 16534472]

Kadambi PV, Josephson MA, Williams J, Corey L, Jerome KR, Meehan SM, Limaye AP. Treatment of refractory BK virus-associated nephropathy with cidofovir. Am J Transplant 2003;3:186–191. [PubMed: 12614296]

Kassem A, Schopflin A, Diaz C, Weyers W, Stickeler E, Werner M, Zur Hausen A. Frequent detection of Merkel cell polyomavirus in human Merkel cell carcinomas and identification of a unique deletion in the VP1 gene. Cancer Res 2008;68:5009–5013. [PubMed: 18593898]

Khalili K, Gordon J, White MK. The polyomavirus, JCV and its involvement in human disease. Adv Exp Med Biol 2006;577:274–287. [PubMed: 16626043]

Khalili K, White MK, Lublin F, Ferrante P, Berger JR. Reactivation of JC virus and development of PML in patients with multiple sclerosis. Neurology 2007;68:985–990. [PubMed: 17389301]

Kleinschmidt-DeMasters BK, Tyler KL. Progressive multifocal leukoencephalopathy complicating treatment with natalizumab and interferon beta-1a for multiple sclerosis. N Engl J Med 2005;353:369–374. [PubMed: 15947079]

Knowles, WA. The epidemiology of BK virus and the occurrence of antigenic and genomic subtypes. In: Khalili, K.; Stoner, GL., editors. Human Polyomaviruses: Molecular and clinical perspectives. Wiley-Liss, Inc; New York: 2001. p. 527-559.

Knowles WA. Discovery and epidemiology of the human polyomavirus BK virus (BKV) and JC virus (JCV). Adv Exp Med Biol 2006;577:19–45. [PubMed: 16626025]

Knowles WA, Pillay D, Johnson MA, Hand JF, Brown DW. Prevalence of long-term BK and JC excretion in HIV-infected adults and lack of correlation with serological markers. J Med Virol 1999;59:474–479. [PubMed: 10534729]

Knowles WA, Pipkin P, Andrews N, Vyse A, Minor P, Brown DW, Miller E. Population-based study of antibody to the human polyomaviruses BKV and JCV and the simian polyomavirus SV40. J Med Virol 2003;71:115–123. [PubMed: 12858417]

Koralnik IJ. Progressive multifocal leukoencephalopathy revisited: Has the disease outgrown its name? Ann Neurol 2006;60:162–173. [PubMed: 16862584]

Koralnik IJ, Boden D, Mai VX, Lord CI, Letvin NL. JC virus DNA load in patients with and without progressive multifocal leukoencephalopathy. Neurology 1999a;52:253–260. [PubMed: 9932940]

Koralnik IJ, Schmitz JE, Lifton MA, Forman MA, Letvin NL. Detection of JC virus DNA in peripheral blood cell subpopulations of HIV-1-infected individuals. J Neurovirol 1999b;5:430–435. [PubMed: 10463865]

Kuypers DR, Vandooren AK, Lerut E, Evenepoel P, Claes K, Snoeck R, Naesens L, Vanrenterghem Y. Adjuvant low-dose cidofovir therapy for BK polyomavirus interstitial nephritis in renal transplant recipients. Am J Transplant 2005;5:1997–2004. [PubMed: 15996251]

Laghi L, Randolph AE, Chauhan DP, Marra G, Major EO, Neel JV, Boland CR. JC virus DNA is present in the mucosa of the human colon and in colorectal cancers. Proc Natl Acad Sci U S A 1999;96:7484–7489. [PubMed: 10377441]

Langer-Gould A, Atlas SW, Green AJ, Bollen AW, Pelletier D. Progressive multifocal leukoencephalopathy in a patient treated with natalizumab. N Engl J Med 2005;353:375–381. [PubMed: 15947078]

Le BM, Demertzis LM, Wu G, Tibbets RJ, Buller R, Arens MQ, Gaynor AM, Storch GA, Wang D. Clinical and epidemiologic characterization of WU polyomavirus infection, St. Louis, Missouri. Emerg Infect Dis 2007;13:1936–1938. [PubMed: 18258052]

Lee W, Langhoff E. Polyomavirus in human cancer development. Adv Exp Med Biol 2006;577:310–318. [PubMed: 16626045]

Leung AY, Chan MT, Yuen KY, Cheng VC, Chan KH, Wong CL, Liang R, Lie AK, Kwong YL. Ciprofloxacin decreased polyoma BK virus load in patients who underwent allogeneic hematopoietic stem cell transplantation. Clin Infect Dis 2005;40:528–537. [PubMed: 15712075]

Liddington RC, Yan Y, Moulai J, Sahli R, Benjamin TL, Harrison SC. Structure of simian virus 40 at 3.8-A resolution. Nature 1991;354:278–284. [PubMed: 1659663]

Lin F, Zheng M, Li H, Zheng C, Li X, Rao G, Zheng M, Wu F, Zeng A. WU polyomavirus in children with acute lower respiratory tract infections, China. J Clin Virol 2008;42:94–102. [PubMed: 18242126]

Major EO, Amemiya K, Elder G, Houff SA. Glial cells of the human developing brain and B cells of the immune system share a common DNA binding factor for recognition of the regulatory sequences of the human polyomavirus, JCV. J Neurosci Res 1990;27:461–471. [PubMed: 1964178]

Major EO, Amemiya K, Tornatore CS, Houff SA, Berger JR. Pathogenesis and molecular biology of progressive multifocal leukoencephalopathy, the JC virus-induced demyelinating disease of the human brain. Clin Microbiol Rev 1992;5:49–73. [PubMed: 1310438]

Markowitz RB, Eaton BA, Kubik MF, Latorra D, McGregor JA, Dynan WS. BK virus and JC virus shed during pregnancy have predominantly archetypal regulatory regions. J Virol 1991;65:4515–4519. [PubMed: 1649346]

Martini F, Iaccheri L, Martinelli M, Martinello R, Grandi E, Mollica G, Tognon M. Papilloma and polyoma DNA tumor virus sequences in female genital tumors. Cancer Invest 2004;22:697–705. [PubMed: 15581050]

Meneguzzi G, Pignatti PF, Barbanti-Brodano G, Milanesi G. Minichromosome from BK virus as a template for transcription in vitro. Proc Natl Acad Sci U S A 1978;75:1126–1130. [PubMed: 26051]

Mengel M, Marwedel M, Radermacher J, Eden G, Schwarz A, Haller H, Kreipe H. Incidence of polyomavirus-nephropathy in renal allografts: influence of modern immunosuppressive drugs. Nephrol Dial Transplant 2003;18:1190–1196. [PubMed: 12748354]

Mininberg DT, Watson C, Desquitado M. Viral cystitis with transient secondary vesicoureteral reflux. J Urol 1982;127:983–985. [PubMed: 7087004]

Monaco MC, Jensen PN, Hou J, Durham LC, Major EO. Detection of JC virus DNA in human tonsil tissue: evidence for site of initial viral infection. J Virol 1998a;72:9918–9923. [PubMed: 9811728]

Monaco MC, Shin J, Major EO. JC virus infection in cells from lymphoid tissue. Dev Biol Stand 1998b; 94:115–122. [PubMed: 9776232]

Monaco MCG, Atwood WJ, Gravell M, Tornatore CS, Major EO. JC virus infection of hematopoietic progenitor cells, primary B lymphocytes, and stromal cells: implications for viral latency. J Virol 1996;70:7004–7012. [PubMed: 8794345]

Monini P, Rotola A, de Lellis L, Corallini A, Secchiero P, Albini A, Benelli R, Parravicini C, Barbanti-Brodano G, Cassai E. Latent BK virus infection and Kaposi's sarcoma pathogenesis. Int J Cancer 1996;66:717–722. [PubMed: 8647638]

Monini P, Rotola A, Di Luca D, De Lellis L, Chiari E, Corallini A, Cassai E. DNA rearrangements impairing BK virus productive infection in urinary tract tumors. Virology 1995;214:273–279. [PubMed: 8525628]

Mori M, Aoki N, Shimada H, Tajima M, Kato K. Detection of JC virus in the brains of aged patients without progressive multifocal leukoencephalopathy by the polymerase chain reaction and Southern hybridization analysis. Neurosci Lett 1992;141:151–155. [PubMed: 1331897]

Muller U, Zentgraf H, Eicken I, Keller W. Higher order structure of simian virus 40 chromatin. Science 1978;201:406–415. [PubMed: 208155]

Munoz P, Fogeda M, Bouza E, Verde E, Palomo J, Banares R. Prevalence of BK virus replication among recipients of solid organ transplants. Clin Infect Dis 2005;41:1720–1725. [PubMed: 16288394]

Neske F, Blessing K, Ullrich F, Prottel A, Wolfgang Kreth H, Weissbrich B. WU polyomavirus infection in children, Germany. Emerg Infect Dis 2008;14:680–681. [PubMed: 18394299]

Newman JT, Frisque RJ. Detection of archetype and rearranged variants of JC virus in multiple tissues from a pediatric PML patient. J Med Virol 1997;52:243–252. [PubMed: 9210031]

Newman JT, Frisque RJ. Identification of JC virus variants in multiple tissues of pediatric and adult PML patients. J Med Virol 1999;58:79–86. [PubMed: 10223551]

Nickeleit V, Hirsch HH, Zeiler M, Gudat F, Prince O, Thiel G, Mihatsch MJ. BK-virus nephropathy in renal transplants-tubular necrosis, MHC-class II expression and rejection in a puzzling game. Nephrol Dial Transplant 2000;15:324–332. [PubMed: 10692517]

Nickeleit V, Mihatsch MJ. Polyomavirus nephropathy in native kidneys and renal allografts: an update on an escalating threat. Transpl Int 2006;19:960–973. [PubMed: 17081225]

Nickeleit V, Singh HK, Mihatsch MJ. Polyomavirus nephropathy: morphology, pathophysiology, and clinical management. Current Opinion in Nephrology and Hypertension 2003;12:599–605. [PubMed: 14564196]

Norja P, Ubillos I, Templeton K, Simmonds P. No evidence for an association between infections with WU and KI polyomaviruses and respiratory disease. J Clin Virol 2007;40:307–311. [PubMed: 17997354]

Padgett BL, Walker DL, ZuRhein GM, Eckroade RJ, Dessel BH. Cultivation of papova-like virus from human brain with progressive multifocal leucoencephalopathy. Lancet 1971;1:1257–1260. [PubMed: 4104715]

Pavlakis M, Haririan A, Klassen DK. BK virus infection after non-renal transplantation. Adv Exp Med Biol 2006;577:185–189. [PubMed: 16626036]

Payungporn S, Chieochansin T, Thongmee C, Samransamruajkit R, Theamboolers A, Poovorawan Y. Prevalence and molecular characterization of WU/KI polyomaviruses isolated from pediatric patients with respiratory disease in Thailand. Virus Res 2008;135:230–236. [PubMed: 18468712]

Pietropaolo V, Fioriti D, Simeone P, Videtta M, Di Taranto C, Arancio A, Orsi N, Degener AM. Detection and sequence analysis of human polyomaviruses DNA from autoptic samples of HIV-1 positive and negative subjects. Int J Immunopathol Pharmacol 2003;16:269–276. [PubMed: 14611731]

Poduval RD, Meehan SM, Woodle ES, Thistlethwaite JR, Haas M, Cronin DC, Vats A, Josephson MA. Successful retransplantation after renal allograft loss to polyoma virus interstitial nephritis. Transplantation 2002;73:1166–1169. [PubMed: 11965053]

Prosser SE, Orentas RJ, Jurgens L, Cohen EP, Hariharan S. Recovery of BK virus large T-antigen-specific cellular immune response correlates with resolution of bk virus nephritis. Transplantation 2008;85:185–192. [PubMed: 18212622]

Quinlivan EB, Norris M, Bouldin TW, Suzuki K, Meeker R, Smith MS, Hall C, Kenney S. Subclinical central nervous system infection with JC virus in patients with AIDS. J Infect Dis 1992;166:80–85. [PubMed: 1318912]

Ramos E, Drachenberg CB, Papadimitriou JC, Hamze O, Fink JC, Klassen DK, Drachenberg RC, Wiland A, Wali R, Cangro CB, Schweitzer E, Bartlett ST, Weir MR. Clinical course of polyoma virus nephropathy in 67 renal transplant patients. J Am Soc Nephrol 2002a;13:2145–2151. [PubMed: 12138148]

Ramos E, Drachenberg CB, Portocarrero M, Wali R, Klassen DK, Fink JC, Farney A, Hirsch H, Papadimitriou JC, Cangro CB, Weir MR, Bartlett ST. BK virus nephropathy diagnosis and treatment: experience at the University of Maryland Renal Transplant Program. Clin Transpl 2002b: 143–153.

Rekvig OP, Moens U, Fredriksen K, Traavik T. Human polyomavirus BK and immunogenicity of mammalian DNA: a conceptual framework. Methods 1997;11:44–54. [PubMed: 8990088]

Rinaldo CH, Hirsch HH. Antivirals for the treatment of polyomavirus BK replication. Expert Rev Anti Infect Ther 2007;5:105–115. [PubMed: 17266458]

Roskopf J, Trofe J, Stratta RJ, Ahsan N. Pharmacotherapeutic options for the management of human polyomaviruses. Adv Exp Med Biol 2006;577:228–254. [PubMed: 16626040]

Safak M, Khalili K. An overview: Human polyomavirus JC virus and its associated disorders. J Neurovirol 2003;9:3–9. [PubMed: 12709864]

Savona MR, Newton D, Frame D, Levine JE, Mineishi S, Kaul DR. Low-dose cidofovir treatment of BK virus-associated hemorrhagic cystitis in recipients of hematopoietic stem cell transplant. Bone Marrow Transplant 2007;39:783–787. [PubMed: 17438584]

Sener A, House AA, Jevnikar AM, Boudville N, McAlister VC, Muirhead N, Rehman F, Luke PP. Intravenous immunoglobulin as a treatment for BK virus associated nephropathy: one-year follow-up of renal allograft recipients. Transplantation 2006;81:117–120. [PubMed: 16421486]

Sessa A, Esposito A, Giliberti A, Bergallo M, Costa C, Rossano R, Lettieri E, Capuano M. BKV Reactivation in Renal Transplant Recipients: Diagnostic and Therapeutic Strategy-Case Reports. Transplant Proc 2008;40:2055–2058. [PubMed: 18675128]

Seth P, Diaz F, Major EO. Advances in the biology of JC virus and induction of progressive multifocal leukoencephalopathy. J Neurovirol 2003;9:236–246. [PubMed: 12707854]

Shah KV, Galloway DA, Knowles WA, Viscidi RP. Simian virus 40 (SV40) and human cancer: a review of the serological data. Rev Med Virol 2004;14:231–239. [PubMed: 15248251]

Shinohara T, Matsuda M, Cheng SH, Marshall J, Fujita M, Nagashima K. BK virus infection of the human urinary tract. J Med Virol 1993;41:301–305. [PubMed: 8106863]

Silverman L, Rubinstein LJ. Electron microscopic observations on a case of progressive multifocal leukoencephalopathy. Acta Neuropathol 1965;5:215–224. [PubMed: 5886201]

Stehle T, Gamblin SJ, Yan Y, Harrison SC. The structure of simian virus 40 refined at 3.1 A resolution. Structure 1996;4:165–182. [PubMed: 8805523]

Stoner GL, Ryschkewitsch CF, Walker DL, Soffer D, Webster HD. A monoclonal antibody to SV40 large T-antigen labels a nuclear antigen in JC virus-transformed cells and in progressive multifocal leukoencephalopathy (PML) brain infected with JC virus. J Neuroimmunol 1988;17:331–345. [PubMed: 2828425]

Stoner GL, Ryschkewitsch CF, Walker DL, Webster HD. JC papovavirus large tumor (T)-antigen expression in brain tissue of acquired immune deficiency syndrome (AIDS) and non-AIDS patients with progressive multifocal leukoencephalopathy. Proc Natl Acad Sci U S A 1986;83:2271–2275. [PubMed: 3008157]

Stratton, K.; Almario, D.; McCormick, M. Immunization safety review: SV40 contamination of polio vaccine and cancer. National Academies Press; Washington, D.C.: 2002.

Sundsfjord A, Osei A, Rosenqvist H, Van Ghelue M, Silsand Y, Haga HJ, Rekvig OP, Moens U. BK and JC viruses in patients with systemic lupus erythematosus: prevalent and persistent BK viruria, sequence stability of the viral regulatory regions, and nondetectable viremia. J Infect Dis 1999;180:1–9. [PubMed: 10353854]

Tada H, Lashgari MS, Khalili K. Regulation of JCVL promoter function: evidence that a pentanucleotide "silencer" repeat sequence AGGGAAGGGA down-regulates transcription of the JC virus late promoter. Virology 1991;180:327–338. [PubMed: 1845829]

Taguchi F, Kajioka J, Miyamura T. Prevalence rate and age of acquisition of antibodies against JC virus and BK virus in human sera. Microbiol Immunol 1982;26:1057–1064. [PubMed: 6300615]

Taoufik Y, Gasnault J, Karaterki A, Pierre Ferey M, Marchadier E, Goujard C, Lannuzel A, Delfraissy JF, Dussaix E. Prognostic value of JC virus load in cerebrospinal fluid of patients with progressive multifocal leukoencephalopathy. J Infect Dis 1998;178:1816–1820. [PubMed: 9815242]

Tornatore C, Berger JR, Houff SA, Curfman B, Meyers K, Winfield D, Major EO. Detection of JC virus DNA in peripheral lymphocytes from patients with and without progressive multifocal leukoencephalopathy. Ann Neurol 1992;31:454–462. [PubMed: 1316734]

Trowbridge PW, Frisque RJ. Identification of three new JC virus proteins generated by alternative splicing of the early viral mRNA. J Neurovirol 1995;1:195–206. [PubMed: 9222358]

Vallbracht A, Lohler J, Gossmann J, Gluck T, Petersen D, Gerth HJ, Gencic M, Dorries K. Disseminated BK type polyomavirus infection in an AIDS patient associated with central nervous system disease. Am J Pathol 1993;143:29–39. [PubMed: 8391217]

Van Assche G, Van Ranst M, Sciot R, Dubois B, Vermeire S, Noman M, Verbeeck J, Geboes K, Robberecht W, Rutgeerts P. Progressive multifocal leukoencephalopathy after natalizumab therapy for Crohn's disease. N Engl J Med 2005;353:362–368. [PubMed: 15947080]

Vats A, Randhawa PS, Shapiro R. Diagnosis and treatment of BK virus-associated transplant nephropathy. Adv Exp Med Biol 2006;577:213–227. [PubMed: 16626039]

Vilchez RA, Butel JS. Emergent human pathogen simian virus 40 and its role in cancer. Clin Microbiol Rev 2004;17:495–508. [PubMed: 15258090]table of contents

Viscidi RP, Clayman B. Serological cross reactivity between polyomavirus capsids. Adv Exp Med Biol 2006;577:73–84. [PubMed: 16626028]

von Einsiedel RW, Samorei IW, Pawlita M, Zwissler B, Deubel M, Vinters HV. New JC virus infection patterns by in situ polymerase chain reaction in brains of acquired immunodeficiency syndrome patients with progressive multifocal leukoencephalopathy. J Neurovirol 2004;10:1–11. [PubMed: 14982723]

Walker, DL. Progressive multifocal leukoencephalopathy. Demyelinating diseases. In: Vinken, PJ.; Bruyn, GW.; Klawans, HL.; Koetsier, JC., editors. Handbook of clinical neurology. Vol. 4. Elsevier Biomedical Press; Amsterdam: 1985. p. 503-524.7 vols

White FA 3rd, Ishaq M, Stoner GL, Frisque RJ. JC virus DNA is present in many human brain samples from patients without progressive multifocal leukoencephalopathy. J Virol 1992;66:5726–5734. [PubMed: 1326640]

Whiteman ML, Post MJ, Berger JR, Tate LG, Bell MD, Limonte LP. Progressive multifocal leukoencephalopathy in 47 HIV-seropositive patients: neuroimaging with clinical and pathologic correlation. Radiology 1993;187:233–240. [PubMed: 8451420]

Williams JW, Javaid B, Kadambi PV, Gillen D, Harland R, Thistlewaite JR, Garfinkel M, Foster P, Atwood W, Millis JM, Meehan SM, Josephson MA. Leflunomide for polyomavirus type BK nephropathy. N Engl J Med 2005;352:1157–1158. [PubMed: 15784677]

Yousry TA, Major EO, Ryschkewitsch C, Fahle G, Fischer S, Hou J, Curfman B, Miszkiel K, Mueller-Lenke N, Sanchez E, Barkhof F, Radue EW, Jager HR, Clifford DB. Evaluation of patients treated

with natalizumab for progressive multifocal leukoencephalopathy. N Engl J Med 2006;354:924–933. [PubMed: 16510746]

zur Hausen H. Novel human polyomaviruses--re-emergence of a well known virus family as possible human carcinogens. Int J Cancer 2008;123:247–250. [PubMed: 18449881]

Zurhein G, Chou SM. Particles Resembling Papova Viruses in Human Cerebral Demyelinating Disease. Science 1965;148:1477–1479. [PubMed: 14301897]

Table 1

Human Polyomaviruses and Disease

Human Polyomavirus	Date of discovery	Major cell type infected	Associated diseases
BKV	1971 (Gardner *et al.*)	Kidney epithelium, Urothelium	Hemorrhagic cystitis (HC), Polyomavirus nephropathy (PVN)
JCV	1971 (Padgett *et al.*)	Kidney epithelium, Lymphocytes, Oligodendrocytes	Progressive multifocal leukoencephalopathy (PML)
KI	2007 (Allander *et al.*)	?	?
WU	2007 (Gaynor *et al.*)	?	?
MCV	2008 (Feng *et al.*)	Merkel cells	Merkel cell carcinoma