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Human Polyoma Viruses and Disease with Emphasis on Clinical BK and JC

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Abstract

Polyoma viruses are ubiquitous infecting many different mammalian species including humans. There are five known human polyoma viruses. JC virus and BK virus are two polyoma viruses identified nearly three decades ago. Recently WU, KI and Merkel cell polyoma viruses have been isolated from humans. The exact role of these three newly discovered viruses in human disease is not known. Most human polyoma disease is caused by BK and JC viruses which are usually acquired in childhood. Approximately 50–80% of humans have seropositivity to these viruses. Clinically apparent diseases in immunocompetent hosts are extremely rare. These viruses remain latent possibly in the lymphoid organs and kidney and under the circumstances of severe immunosuppression both these viruses reactivate. Neurotropic JC virus reaches the brain and causes progressive multifocal leukencephalopathy, a demyelinating disease of the central nervous system with a high mortality rate. BK virus is urotheliotropic and its reactivation causes a form of interstitial nephritis, known as BK or polyoma virus associated nephropathy which is associated with high graft loss if not recognized early. There are no known effective antiviral agents for any of the polyoma viruses.

Keywords

Polyomavirus; BK virus; JC virus

Introduction

The first polyoma virus, Murine K virus, was described by Lawrence Kilham in 1952[1]. Subsequently, Ludwik Gross identified the mouse polyoma virus (MPyV) producing small tumors in new born mice[2]. He inoculated murine leukemia virus into newborn mice producing leukemia and parotid adenocarcinomas. Cell free extracts from the parotid glands produced a variety of solid tumors. These viruses were later named by Steward and Eddy as polyoma virus in 1958 as they have propensity to produce a variety of solid tumors in newborn mice[3, 4]. Simian polyoma virus, simian vacuolating virus (SV40), which infects

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rhesus monkeys was identified by Bernice Eddy, Ben Sweet and Maurice Hilleman, as the contaminant of Salk human polio vaccine[5]. Padgett et al identified JC virus (JCV) as the infective agent in a patient, John Cunningham (initials JC), with Hodgkin's lymphoma who suffered from progressive multifocal leukoencephalopathy (PML) in 1971[6] . During the same year, BK virus (BKV) was isolated by Sylvia Gardner from urine of a Sudanese kidney transplant patient with ureteric stenosis whose initials were BK[7].

KI polyoma virus (KIPyV) and WU polyoma viruses (WUPyV) were identified in 2007 from respiratory secretions of patients with respiratory infections by Allander and Gaynor et al respectively[8, 9]. KI and WU viruses are named after the institutions where they were initially isolated. In January 2008, Feng, et al, identified Merkel cell polyoma virus (MCPyV) which has been associated with Merkel cell carcinoma[10]. With the identification of the MCPyV, currently, known polyoma viruses include 16 different viral species and infect 8 different mammalian species[10, 11] (Figure 1). Natural hosts for these viruses are humans, monkeys, rodents, cattle, rabbits and birds. These viruses are fairly species specific and do not readily infect other species[12]. The two viruses that can cause significant diseases in humans are BK virus which causes an interstitial nephritis, known as BK virus nephropathy (BKVN) or polyoma virus associated nephropathy (PVAN) and JC virus which causes PML in AIDS and other immunosuppressed patients. We review the biology, life cycle, and epidemiology of the human polyoma viruses in general and focus on the diagnosis and management of BK and JC disease.

Biology of Polyoma viruses

The genus of polyoma viruses belongs to the Papovavirdae family. Polyoma viruses are icosahedral, non-enveloped double stranded circular super coiled viruses. They measure 40.5 – 44 nm in diameter and comprise 88% protein and 12% DNA[13]. The viral DNA genome has around 5000 base pairs organized in three different functional regions: the early coding and late coding regions separated by a non-coding regulatory region (NCCR)[12, 14, 15]. The NCCR encompasses the origin of DNA replication (ori) and has transcription control factors which direct the expression of both early and late genes[12, 14]. The early coding region is transcribed before DNA replication and encodes the large tumor antigen or "T antigen" and small tumor antigen or "t antigen". The late coding region is transcribed after DNA replication and encodes viral protein 1 (VP1), VP2, and the VP3 capsid proteins and the agnoprotein. The outer shell of the virion has 72 pentamers of which VP1 is the major capsid protein and each pentamer is associated with a single copy of VP2 or VP3 which are minor capsid proteins[16, 17, 18]. The C-terminals of the VP1 molecule attach to each other and to the neighboring capsomere forming a complete capsid[19, 20]. The "large" T antigen is thought to play an important role in infection[13]. The human polyoma viruses share 69 to 75% DNA sequence homology with SV40 which may cause human disease. The protein sequence homology is greater at 76 to 90%[21].

The BKV genome has 75% homology to JCV and 70% homology to SV40. The WUPyV and KIPyV share homology with the BKV and JCV genomes[8, 9] whereas MCPyV is similar to the African green monkey lymphotropic virus[10] (Figure 1). In JCV, BKV and SV40, the late coding region also encodes the agnoprotein which aids viral assembly and release[14]. The agnoprotein is absent in KIPyV, WUPyV and MCPyV[8, 9, 10]. The viral genome is associated with cellular histones to form mini chromosomes, with a structure similar to host chromatin[13]. Four main JCV types have been identified: type 1 in Europeans, type 2 in Asians, type 3 in Africans and type 4 in US populations[22]. Four serologic subtypes of BK virus are identified by the Roman numerals I, II, III, IV but the significance of the different subtypes is unclear[23, 24].

Polyoma virus life cycle

Each virus requires a specific receptor for cellular entry, which explains their tissue tropism and species specificity. SV40 uses the ganglioside GM1 and a receptor that belongs to the MHC class I protein[11, 25]. BK uses an N-linked glycoprotein containing alpha (2, 3) linked sialic acid, GT1b, GD1b whereas MPyV uses GD1a and GT1b as the receptors[26, 27, 28]. Cells treated with neuraminidase limit BKV infection in vitro. The JC virus uses alpha (2, 6) linked sialic acid associated with the serotonin 5HT2A receptor. Treating cells with a 5HT2A receptor antagonist restricts JCV infectivity in vitro[29]. Receptors of the remaining polyoma viruses are yet to be identified. As these are non-enveloped viruses they enter the cell through endocytosis[30]. The JC virus uses clathrin-coated pits and BK, SV40 and MPyV virus use caveolae which are invaginations of the cell membrane[31, 32, 33]. Once internalized through endocytosis, the JC virus reaches endosomes, and from endosomes they reach caveosomes in a pH dependent manner[32, 34]. After SV40 enters the cell through endocytosis viruses are picked up by caveosomes, from there the virus reaches the endoplasmic reticulum in a microtubule dependent manner with the help of tubular vesicles[34]. BK may use a similar pathway for trafficking[35]. At least two of the polyoma viruses SV40 and MPyV use endoplasmic reticulum associated degradation pathways for uncoating and translocating from endoplasmic reticulum into cytosol[26, 36, 37, 38]. The low calcium content of the cytosol helps in further disassembly of the un-stable virion. The VP1 protein particles help in localizing the nuclear pore and entry in to the nucleus. Within the nucleus early transcription of T and t antigens happens first followed by DNA replication secondly and then late gene expression for the capsid proteins. Lastly, virions are assembled and progeny are released through lytic destruction of the cell.

Epidemiology of Polyoma viruses

The prevalence of BK and JC viral infection differs in geographical and age distribution suggesting they circulate independently[39]. BK infection is acquired in early childhood whereas JC presents later, 3–4 years versus 10–14 years[40, 41, 42]. Approximately 80% of the adult population is seroprevalent for polyomaviruses[40, 41, 42]. The mode of transmission of these viruses is not well known. Transmission through the feco-oral and respiratory routes has been suggested[43, 44]. Other routes include blood transfusion, transplacentally, through semen, and organ transplantation[45, 46]. Transmission occurs mostly through close contact[47]. Primary infection mainly occurs in childhood and is asymptomatic or minimally symptomatic. Asymptomatic shedding of these viruses in the urine can be seen in both healthy subjects and immunosuppressed patients[48], with asymptomatic JC and BK viruria seen in 3% of pregnant patients. In the general population, JC viruria is more common than BK viruria[49]. In a recent study of healthy Swiss blood donors the incidence of JC and BK viruria were 19% and 7%, respectively[50]. In contrast, in immunocompromised patients, BK viruria is more common[51].

Clinical Diseases

After initial infection, both BK and JC viruses remain latent in different tissues (*vide infra*). For unknown reasons, BK viruria correlates with degree of immunosuppression whereas JC viruria does not. BK virus can cause pneumonitis, hepatitis, retinitis, and meningoencephalitis[52]. Hemorrhagic cystitis from BK virus is seen in 25–60% of the bone marrow transplant patients (BMT)[53, 54, 55]. It is usually seen two weeks after transplant which is later than the hemorrhagic cystitis from chemotherapeutic agents such as cyclophosphamide which occurs immediately[54]. Symptoms include dysuria, urgency, frequency, suprapubic pain and varying degree of hematuria. The diagnosis is made by detecting BK viral DNA in the urine. Treatment is usually supportive with hyperhydration,

forced diuresis, bladder irrigation and transfusion as indicated. If the hematuria is severe with clots, cystoscopy and clot removal and cauterization of the source might be needed. Recent studies show that some BMT patients who received prophylactic ciprofloxacin, have decreased peak urine BK viral load and less severe hemorrhagic cystitis[55].

The KIPyV, WUPyV viruses were isolated from patients with respiratory infections, but the role of these viruses in the etiology of human infections needs to be further investigated. SV40, although not a human polyoma virus, produces malignant mesotheliomas in hampsters and has been seen in human malignant mesothelial cells[56]. However, more recent studies do not support an association between human malignant mesothelioma and SV40[57, 58]. Merkel cell carcinoma is an aggressive neuro-endocrine skin cancer, originating from the mechano-receptor Merkel cell. It is noted to be more common in immunosuppressed states suggesting an infectious etiology[59]. Feng et al identified MCPyV DNA in Merkel cell carcinoma patients and also noted viral DNA clonally integrated into the tumor genome[10]. Others have since noted similar associations between MCPyV and Merkel cell carcinoma, however, the exact causative role of MCPyV in Merkel cell carcinoma requires future study[59].

BKV Nephropathy

After primary infection in childhood BK virus becomes latent in the tubular epithelial cells of the urogenital tract[51]. It mainly affects epithelial cells of collecting ducts, tubular epithelium of renal calyces and renal pelvis[60]. In immunosuppressed states BK may reactivate in the renal tubular epithelial cells causing necrosis and lytic destruction with denudation of the basement membrane allowing tubular fluid to accumulate in the interstitial compartment, which in turn causes interstitial fibrosis and tubular atrophy[61]. Up to 80% of renal transplant patients have BK viruria and 5–10% progress to BKVN[62, 63, 64]. Use of newer potent immunosuppressive agents such as mycophenolate mofetil (MMF) or tacrolimus has been implicated in the recent emergence of this infection[62]. However it is seen with most of the other immunosuppressive agents such as cyclosporine and sirolimus[65, 66] and the consensus is that that degree of immunosuppression rather than the type of immunosuppression that predisposes to BKVN[67].

Viral reactivation starts soon after transplantation and is seen in 30–50% of the patients by 3 months post transplant[63, 68]. When the virus, reactivates it can present as asymptomatic deterioration of renal function, tubulo-interstitial nephritis, and ureteric stenosis[7, 64, 66, 69]. Reported risk factors for BK infection include higher intensity of immunosuppression, prior tubular injury from rejection or drugs, surgical injury, warm ischemia and reperfusion injury during implantation of the graft, higher HLA mismatches, seronegativity of the recipient[61, 67, 70]. Other significant risk factors may include older age, white race, male gender, diabetes, lack of HLA-C7 and deceased donor transplantation[46, 71, 72].

A combination of factors is thought to play a pathogenic role[73]. Cell-mediated immunity might be important as low levels of interferon-gamma secreting T lymphocytes specific for BK virus correlate with higher levels of BK viremia and BKV nephropathy[74]. Humoral immunity is less important as seropositivity is not protective and recipients of donors with higher antibody titers are more likely to have BK reactivation indicating donor origin or the virus[46, 75]. The disease passes though three progressive stages, viral DNA can be seen first in the urine then in the plasma and lastly in the kidney[68, 72, 76]. Progression of viruria to viremia occurs in 10–15% of kidney transplant patients, and sustained viremia is a harbinger of interstitial nephritis[51, 68, 77]. BK nephropathy is suspected with signs suggestive of interstitial nephritis. It typically presents 10–13 months post transplant and graft failure rates can be as high as 50–80% depending on the degree of inflammation and fibrosis seen on the

biopsy[78]. BK nephropathy is extremely rare in the native kidneys of non-renal solid organ transplantation despite comparable or higher levels of immunosuppression, suggesting that BKVN is donor derived or other factors specific to the transplanted kidney play a role[46, 71, 79, 80]. Re-transplantation can be successfully performed and usually after the virus has cleared[51].

Progressive Multifocal leukoencephalopathy (PML)

Progressive Multifocal leukoencephalopathy is a progressive demyelinating central nervous system disorder involving cerebral white matter caused by the JC virus[81]. It most often presents as an opportunistic infection in HIV patients with lymphopenia but has recently been seen with new immunosuppressives *(vide infra)*. Typical PML patients have very low CD4 T-cell counts even less than 200 per cubic mm. PML also seen in other immunosuppressed states such as myeloproliferative and lymphoproliferative disorders, patients treated with purine analogues such as fludarabine[82], granulomatous infections and natalizumab used to treat multiple sclerosis and Crohn's disease[83, 84]. The Food and Drug Administration issued warnings in 2009 regarding use of rituximab, an anti-CD20 antibody, and MMF which had recently been found associated with PML.

The seroprevalence of JC is high with 80% of humans having positive antibodies to JCV indicating prior infection[85]. After the initial infection the virus remains latent in the lymphoid organs, kidneys and in severely immunosuppressed states the virus travels to the central nervous (CNS) system through infected B-lymphocytes[85, 86] where it produces lytic destruction of myelin producing glial cells, i.e. oligodendrocytes and non lytic infection of astrocytes, causing progressive disease in the CNS[6, 81, 83].

The estimated incidence of PML in HIV patients is 5%[87] but is decreasing with the introduction of highly active anti retroviral therapy (HAART)[88]. Clinical manifestations of PML include confusion, mental status changes, gait ataxia, focal neurological deficits such as hemi paresis, limb paresis and visual changes[81, 89]. PML usually affects the sub-cortical and cortical white matter, and clinical symptoms vary depending on the area of involvement. PML can affect cerebral hemispheres, brain stem and cerebellum. A variant of classical PML is "inflammatory PML" which is seen in HIV patients with improved CD4 counts and reduced HIV viral loads on HAART. Inflammatory PML can present as new PML or worsening of existing PML[84]. Although the initial presentation is worse, outcomes are favorable compared to classical PML[90]. JC virus can also affect granule-cells of the cerebellum causing cerebellar atrophy and ataxia known as "JCV granule-cell neuronopathy"[91].

PML usually presents neuroradiologically as asymmetrical, well demarcated lesions of white matter demyelination which do not enhance with contrast or show mass effect[92]. Brain MRI can show high intensity on T2 weighted images and fluid attenuated inversion recovery images or low intensity in T1 weighted images. The prognosis is grim. The average survival of patients with HIV is only a few months[93], however with HAART therapy mortality rates have been reduced (0.4 years before HAART and 1.8 years after HAART). There is no specific antiviral agent.

Polyoma virus diagnosis

BK

A diagnosis of BKVN requires a biopsy but can be suggested or supported by detection of viral replication in urine or blood. Urine of patients' with BKVN may show "Decoy cells" which are infected renal tubular epithelial cells with intranuclear basophilic inclusion bodies

seen on Papanicolaou stain[51, 94]. Decoy cells have 100% sensitivity but a positive predictive value of only 20%[62, 95]. BK viral replication can be documented by urine or blood BK viral DNA polymerase chain reaction (PCR) or urine mRNA-PCR. Detection of anti-BK virus antibodies are not helpful and viral culture is not used.

An international consensus panel recommends screening for BK virus every 3 months for the first 2 years after transplant or when allograft dysfunction occurs[71] with urine decoy cells, urine BK virus DNA or urine mRNA for VP1. If positive, confirmatory tests with blood or urine quantitative DNA PCR or urine PCR for mRNA for VP1 need to be done. If the thresholds for the confirmatory tests (Urine BK DNA $>1 \times 10^7$, Plasma BK DNA $> 1 \times 10^4$ and urine mRNA for VP1 $>6.5\times 10^5$) are met, allograft biopsy should be considered in the absence of evidence of renal dysfunction. We prefer to monitor only the blood since asymptomatic BK viruria is common[70]. The strategy of monitoring BK viral replication and reduction of immunosuppression has been shown to prevent progression to BKVN[68, 70, 96]. In a recent study screening for BK virus with urine Decoy cells or plasma BK PCR over a 2-year follow up was cost-effective with savings realized from reduction in immunosuppression in BK viremic patients[97].

As BK infection resembles acute rejection on biopsy it is essential to differentiate BKVN from rejection as inappropriate treatment will result in the loss of the graft[73]. Allograft biopsy remains the gold standard modality for diagnosis[98] showing characteristic cytopathological changes in renal tissue confirmed by positive immunohistochemistry using antibodies directed specifically against BK virus or the cross reacting SV40 large T antigen. Since it has a patchy distribution affecting mostly the medulla, two core biopsy samples including medulla should be obtained[51]. Positive staining for SV40 is pathognomonic for BK nephropathy. Recently, the use of electron microscopy to detect cast-like, three-dimensional polyomavirus aggregates in urine called “Haufen” has been found to be sensitive and specific for BKVN[99]. The positive and negative predictive values of Haufen for BK polyomavirus nephropathy were 97% and 100%, respectively.

JC

The differential diagnosis for PML is HIV associated encephalopathy and primary CNS lymphoma. HIV associated encephalopathy presents with cognitive, motor and behavioral problems and brain lesions are symmetrical, poorly demarcated and involve peri-ventricular areas with cerebral spinal fluid (CSF) analysis negative for myelin basic protein and JC virus PCR[87]. CNS lymphomas have mass effects, edema and post contrast enhancement and often have positive CSF cytology or positive Epstein - Barr virus PCR in the CSF. Brain biopsy is the gold standard for diagnosis and has a sensitivity of 64–96%[100]. However, brain biopsy has significant morbidity and mortality, the lesions are not always accessible[101]. A brain biopsy usually shows loss of oligodendrocytes and the remaining oligodendrocytes have enlarged nuclei and reactive gliosis, bizarre multinucleated astrocytes[81, 84, 89] Staining with immunohistochemistry using antibodies directed to SV40 T antigen is confirmatory. Analysis of CSF for JCV DNA by PCR has a sensitivity of 72–92% and a specificity of 92–100%[102]. Some HIV patients who have clinical and radiological features of PML may not have a positive JCV DNA PCR. This is possibly from the decreased JC viral burden in the CSF seen with the immune reconstitution syndrome with the improvement in the CD4 counts[103]. After excluding HIV encephalopathy, CNS lymphoma and toxoplasmosis, a diagnosis of possible PML should be made in patients with clinical and neuro-radiological features of PML, and the patient treated accordingly[104]. PML is very progressive and damaged areas cannot “re-myelinate” resulting in chronic adverse neurological sequelae[84, 88].

Treatment

BK

The first line of treatment of BK virus nephropathy is reduction of immunosuppression[51, 71]. There are no fixed guidelines for the reduction of immunosuppression as there are only a few controlled studies. We have shown that immediate withdrawal of the anti-metabolite upon detection of BK viremia is a safe and effective preemptive strategy to prevent progression from viremia to clinical nephropathy without increasing the risks for acute rejection[68]. Ancillary therapy with antiviral agents is not clear as there is a paucity of data and there are no randomized clinical trials. Drugs with reported in vitro activity against BK virus such as cidofovir, leflunomide or quinolones have been used in combination with immunosuppression reduction with some reported-success[105, 106]. The general consensus is these agents are ineffective in vivo and fraught with side-effects[70]. There is a Phase I-II clinical trial which is just beginning investigating the use of lipid-conjugated cidofovir for BK. The drug may be taken orally and has activity not only against BK but also small pox and the herpes viruses (Chimerix, ClinicalTrials.gov identifier: NCT00793598).

JC

For patients with PML and HIV initiation or optimization of HAART needs to be implemented to decrease viral replication[107]. In non HIV patients with PML such as organ transplant patients, immunosuppression needs to be decreased or stopped[108]. In inflammatory PML, steroids may be used[109]. There is no specific antiviral agent for JC virus. Mefloquine, an oral antimalarial drug, is now undergoing clinical trials for PML (Biogen Idec, ClinicalTrials.gov Identifier NCT00746941).

Role of Polyoma virus in malignancy

As above, there may be a role for polyomaviruses in human malignancy. Polyomaviruses produce tumors in rodents and transform cell lines, and polyoma proteins have been identified in several different human cancers. Polyoma viral proteins interact with regulatory proteins such as p53 and p Rb, cyclins, cyclin dependent kinases etc[110]. However the exact causative and oncologic potential to humans except for Merkel Cell tumor is controversial in the recent literature.

Summary

Polyoma viruses are widespread and affect 80% of the human population. They do not cause clinically significant infections in immunocompetent hosts. The two most common polyoma viruses that cause clinically significant diseases in humans are JCV causing PML and BKV causing BKVN. Further studies are needed to firmly establish the role of polyoma viruses in human cancer. There is no known effective anti-viral agent although two new trials which hold promise are just beginning.

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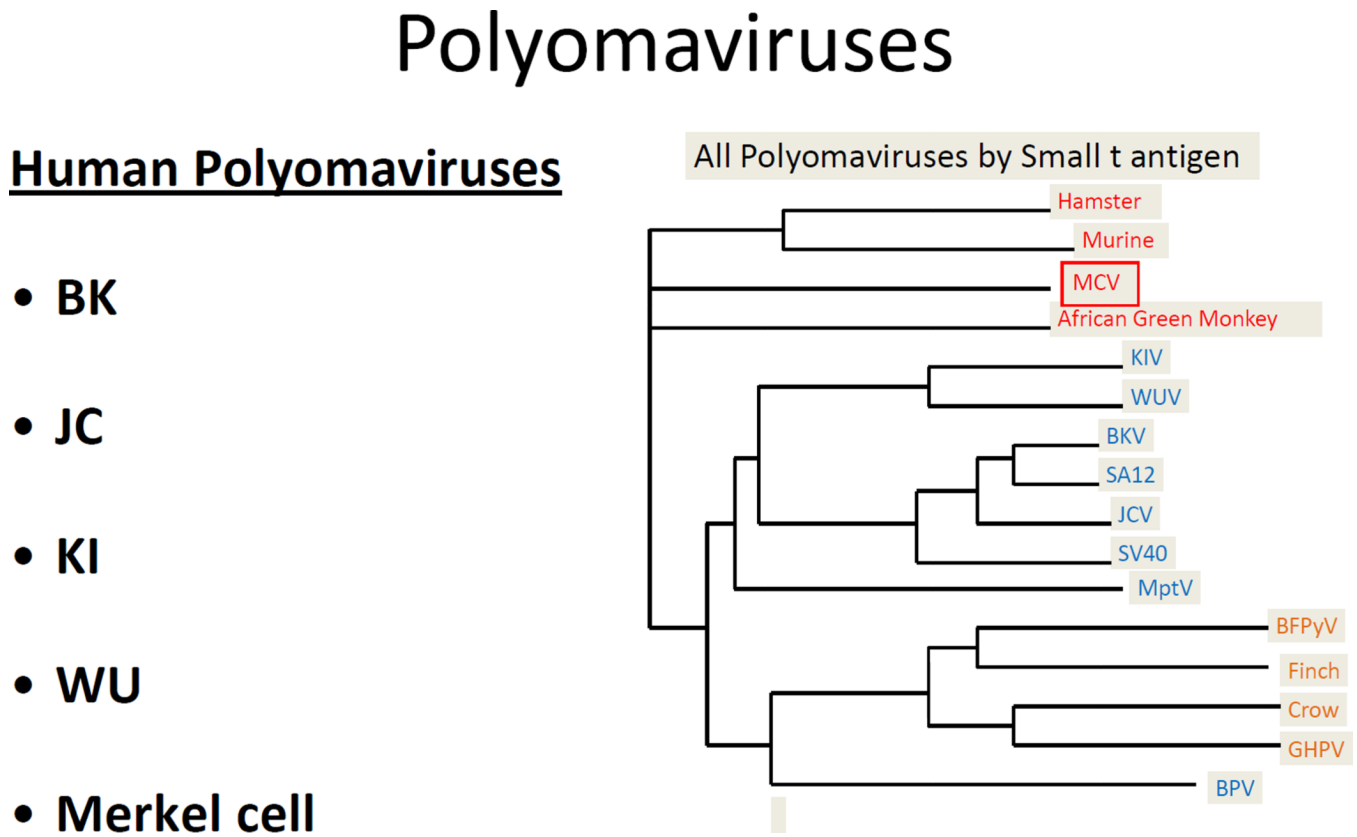

Figure 1. Neighbor-joining trees for the polyoma viruses with the putative MCV based on small T proteins

The four previously known human polyomaviruses (BKV, JCV, KIV and WUV) cluster together in the SV40 subgroup (blue) while MCV is most closely related to MuPyV subgroup viruses (red). Both subgroups are distinct from the avian polyomavirus subgroup (orange). Adapted from Feng H et al., Science 2008; 319:1096 with permission.