Review Article

Characteristics, transmission and pathogenesis of human Polyomavirus: A Review

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Abstract

The family Polyomaviridae contain about a number of human polyomaviruses (HPyVs), of which JCV, MCPyV, SV-40 and BKV viruses have been reported to cause many types of cancer in human. Merkel cell carcinoma is a very antagonistic type of skin cancer caused by the MCPyV5. Similarly, while JCV and SV-40 viruses developed brain tumour cancer, the BK virus has been bind to renal transplantations, prostate cancer and nephropathy producing urinary bladder tumor in human. The name of the family Polyomaviridae, derives from the observation that cells infected with murine polyomavirus produced multiple (poly) tumor (omas) in immune compromised mice. Although, present proof only supports to the role of MCPyV as a carcinogen in to the humans. In the present review we present a summarized discussion on the current knowledge regarding the role of JCPyV, TSPyV, BKPyV and MCPyV in human cancers.

Keywords: Polyomavirus, carcinoma, polyomaviridae, popovav

Introduction

Polyomavirus is the sole genus of viruses inside the Polyomaviridae family. At the starting, polyomaviruses were taxonomically classified as a genus of the Papovaviridae family with papillomaviruses; While, in 2000 the International Committee on Taxonomy of Viruses conventionally split the viruses into two new families, e.g. Polyomaviridae and Papillomaviridae families (Figure 1).

Discovery

Polyomaviruses was first find out in the 1950s in the rodent tissues as named tumour-associated virus. As its name hinted, it has been causes various types of tumours in rodents. On the other side, SV40 was discovered in a monkey cells line that was used in the 1960s for poliovirus vaccine manufacturing. Actually it is believed that a significant number of people had been unintentionally infected by SV40 that was accidentally contained in the vaccine formulation. As per the survey that SV40 causes tumours in rodents lead to a understanding of SV40 is associated to the rodent polyomavirus. Additionally, the discovery of a monkey polyomavirus (i.e., SV40)

Figure 1. Bk polyoma virus (Major, 2001)

vigorously supported a notion that a related virus could also be found in humans as well. The first polyomavirus discover was the mouse polyomavirus (mPyV)(Steward and Eddy, 1958) causing the development of multiple tumour category when immunize into new-born mice. Eventually, many polyomaviruses have been start to infect a diversity of vertebrate species, counting rabbits, rodents, birds, nonhuman primates, and, to date, nine polyomaviruses have been isolate in humans. The range of hold species for every one polyomavirus is very small, and the fertile infection is little to natural host (Major, 2001).

Biology Polyomavirus

The genomes of PyVs can be categorised into three types: the control region; the early region, which carry early proteins; and the late region, which carry late proteins with structural function. The control region includes the origin

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of replication and the stimulator that maintained the expression of early and late genes. Although these regions does not encode any protein or functional RNA. This region is involved in the maintenance of the life cycle of virus by modulating replication and transcription. Both strands of the PyVDNA code for proteins. Early genes are expressed by one strand instantly after infection. On the other side, late genes are expressed by the antagonistic strand after viral genome replication. The mRNA transcribed by both early and late regions present in at least two identical isoforms because of alternative processing. Additionally the expression of a viral micro-RNA has been noticed in the John Cunningham BK polyomavirus (BKPyV) and Merkel cell polyomavirus (MCPyV), polyomavirus (JCPyV), (Paulson et al., 2011; Bauman et al., 2011) This micro-RNA is encoded by the complementary DNA strand to the large antigen-T and, at least in MCPyV, this RNA appears to modulate the expression of these viral proteins (Paulson et al., 2011). The proteins coded with the early genes are incorporate in the genome replication and regulation of viral transcription. The proteins are known as "antigens-T" and accept this DOI: 10.6061/clinics/2018/e558s name due to they were accept by antibodies from rodents causing tumours. Different T-antigen isoforms present and are named based on the viral species by which they produced. The transforming potentiation of the viral category is closely related to the expression of T-antigens and was initially discovered in studies using simian virus 40 (SV40) (Butel and Lednicky, 1999). The large T (LT) antigen is a nuclear protein that is near about 700 amino acids. Although, modification in its phosphorylation pattern may convert the location of this protein in the cell (Howes et al., 1996; Tyagarajan et al., 2006). The LT-antigen maintained both the viral transcription and genome replication (Assetta and Atwood, 2017). Additionally, the LT-antigen as well as the other T-antigen isoforms expressed in human and animal PyVs are pleiotropic proteins that influence the expressions and functions of the number of cellular proteins involved in the maintenance of cell proliferation. The counter balance of the functions of the proteins is critical for the initiation of the entrance of the host cell within the cell cycle, Assemble the DNA replication machinery available and permitting viral genome replication (Sawai and Butel, 1989; Hahn et al., 2002). The late region caring the genes encoded with the structural proteins present in the viral capsid, included VP1 and VP2. Other species also express the structural proteins VP3 and VP4. VP2 and VP3 are required for viral entry into the host cell. Although, the functions of VP4 during the viral life cycle remains a matter of debate. Previous studies have suggested that VP4 serve as a voporing to disrupt the nuclear membrane and mediate viral release (Raghava et al., 2013; Daniyal et al., 2007). Although, in a recent study, Henriksen et al.

showed that human renal proximal tubule epithelial cells transfected with BKPyV genomes carrying start codon substitutions in VP4, predicted to disrupt the production of these proteins are released comparable concentration of viral particles in the supernatant as cells transduced with WT genomes (Henriksen et al., 2016). It can be seen that more studies are needed to determine the role of VP4 in PyV biology. Additionally, some other PyVs, including JCPyV, BKPyV and SV40, contains an open reading frame (ORF) that encodes a administrative cytoplasmic protein named agno-protein (Okada et al., 2001). The participation of agno-protein in viral evolution has been demonstrate in species which express these proteins, including, SV40, JCPyV and BKPyV (Saribas et al., 2016). Study conducted in the previous two decades have exhibits that the expression of VP1 in differ systems promote to the production of structures known as virus-like particles (VLPs), which are same as the viral capsid (Burkert et al., 2014; Touze et al., 2010). After it has expressed, the structural proteins assembled in the cellular nucleus, contributing to the observing of the virion. These proteins are found in different concentration in viral capsids, with VP1 is the important protein in the production of pentamers. The carboxyl end of VP1 expand outside the pentamer and interacts with neighbouring pentamers. These interactions, stimulated by VP1 coupled with Ca²⁺ and disulphide bonds, participate in the stabilization of the capsid structure and capsomers (Imperiale et al., 2007).

BKPYV characteristics

Polyomavirus infections, including BK virus, are large spread both in grow and growing countries (Johne et al., 2011; Knowles, 2006). It is evaluate that near about 90% of the whole population has antibodies against BKPyV particles. These high percentage may be interconnected to the period when the primary infection occurs, generally in early childhood. Although, immediately later birth, maternal antibodies remain for the first few months, so, between the age of 4 and 11 months, antibodies are presence only in 5% of infants (Knowles, 2006). With consider to BKPyV, virus transference routes are not entirely accept. It is presume that infection is transfer via the faecal-oral tract, respiratory tract the blood, or through organ transplant. In case of the usual immune system, infection is asymptomatic, occasionally manifested by a mild inflammation of the upper respiratory tract, a small urinary tract disorders and increase in body temperature. As a result of reproductive infection, the virus move to the latent stage, where urinary tract cells are the major site of perseverance. Exclude for the urinary tract, BKPyV also localize in peripheral blood mononuclear cells

(PBMC), tonsils and hematopoietic tissues (Rynans et al., 2011). A moderately impaired immune system, usually observed in the older, in pregnant women and diabetics, can begin active virus replication. Still, in case of impaired immunity accompanied by in-depth immunosuppression therapy such as in organ transplantation or through acquired immunodeficiency syndrome (AIDS), evident clinical infection transpire (Hirsch et al., 2013; Matlosz et al., 2006). Most often, notice is paid to three types of pathologies coupled to BK virus infection: ureteral stenosis and interstitial nephritis in patients after renal transplantation, also haemorrhagic cystitis in patients after (Matlosz., 2006).

Cell Transformation Mechanism

Three mechanisms of HPyV infection effect on the cancer growth can be distinguished: hit-and-run, traveller and by-stander. In the first, the hit-and-run process, a cell is spread disease with polyomavirus at the first stage of neoplasia. These results in the increase of chromosomal instability (CIN) and stabilize the action of carcinogenesis. Although, in the advanced form, in the route of diagnosis, the virus genetic material is not discover. In the passenger process, the virus affect on the tumour cell where it detect suitable conditions for its genome replication, but it do not have direct effect on cancer development. It can, however, harmful side effects, like cell carcinogenic and weakening facilitation. The last, the by-stander process, does not affect on the mechanism of ontogenesis. Alternatively, the virus infects cells adjoining to tumour cells and is find out in anatomically attached section of these cells (Dalianis and Hirsch, 2013) (Figure 2).

A further role in the mechanism of carcinogenesis is played by one of the functional parts of the genetic matter of virus, the early zone which encodes two non-structural proteins: the small-t antigen (t-Ag) and wide T-antigen (T-Ag). T-Ag is important in initiate cell modification and their limitless proliferation due to its effecting on proteins formulate by the hold. Polyomavirus genomes does not code replication proteins, and, so, they use proteins produced by the effect on cell in the S phase of the cell cycle. T-antigen is affianced in the process of taking control over the cell by interrupt the activity of suppressor proteins: p53 and pRb (Retinoblastoma protein)(White and Khalili,2004). The hindrance of TP53 gene coding p53 protein takes place in around 50% of all cancers. T-Ag of BK virus linked to p53 protein causing its deactivation, thus incapacitate the cell dividing cycle inhibition, which, in consequence , results in an limitless number of divisions. The excluded of apoptosis process is especially for providing the optimal environment for the genetic matter of virus multiplication and the submission of new virions. This action facilitates modification in not permissive cells and supports lytic infection in permissive to cells (White and Khalili, 2004). The pRb (Retinoblastoma protein), belonging to family of the pocket

Figure 2. Cell transfer Mechanisms (Dalianis and Hirsch, 2013)

proteins, is responsible for preventing the E2F factor (from the family of transcription factors) which is important for cell transition through the G1/S inspect point. In case of DNA damage, the phosphorylated active pRb protein linked to E2F, blocking the further cell division. generally, in the course of a usual cell cycle, at the end of the G1 phase, CDK6 and CDK4 cytokines phosphorylate pRB protein. Its deactivation results in evolved transcription factors, which allowing for the S phase of cell division. In the infected cell, in spite of the genetic material modification, the cell cycle is not prevented.. This comes about from the capability of T-Ag viral linking to pRb, which causes the evolved of E2F influence and the cell cycle progression in spite of the occurring changes. It is the main process used by the virus due to which T-Ag approval the abnormal proliferation of transformed cells of oncogenic character (White and Khalili, 2004).

The next process depends upon taking control over the gene of DNA-methyl-O-transferase (DNMT1), being the target gene for the E2F transcription factor. Its overexpression is related to the cancer suppressive gene, hyper methylation, which can result in ontogenesis development. It has been intent on that antigen-T of human BK polyomavirus and E1a adenovirus are able of strong activation of transcription from the DNMT1 promoter. This activation requires Rb protein deactivation by oncogene and then the activation of E2F factor release. Results of this research, coupled with earlier research on DNMT1 overexpression effects, advice to that the abnormal

regulation of DNA thiol transferases activity by pRb/E2F can be important, not only in viral lytic infections, but also in virus induce modification and cancer growth. In the case of virus sudden changing in gene incapable of linking pocket proteins (RB), the deficiency of efficacy in DNMT1 activation is observed, comparison with their wild type equivalents. In addition, E2sudden changing in gene inside DNMT1 promoters considerably neutralize transcription activation. These reported data advice that DNMT1 viral induction via pRB/E2F route modulation can result in cancer modification (McCabe et al., 2006).

Mode of transmission

Serologic studies exhibit large spread prevalence of BK virus infection in man (Smith et al., 2004). Proof is collecting that this is the result of multiple routes of infection (Randhawa and Ramos, 2007; Randhawa and Vats, 2002). Air borne transference is support by observations that BK virus DNA is detect in 1% of nasopharyngeal aspirates acquired from infants with respiratory infection. The chance of feco-oral transference is suggested by demonstration of BK polyoma virus DNA in metropolitan sewage, and in stool test from hospitalized children and bone marrow transplant receiver (Vanchiere et al., 2005). Given that polyomavirus is largely latent in the kidney, renal transplantation is believe to be an important mode of infection in patients with last stage kidney disease (Boldorini et al., 2005). The presence of higher titer anti-VP-1 DNA antibodies in donor serum is coupled with higher risk of virus transmission and disease in the renal allograft recipient. Finally, it is proved that trans placental transmission of polyomavirus can also occur. The frequency of viral reactivation in pregnancy has been variably estimated from rare to as high as 65% (Kalvatchev et al., 2008).

Clinical manifestations

Initial infection, typically during childhood, is not connected with any well-defined clinical syndrome however there are anecdotal report of upper respiratory infection and acute cystitis. After resolution of initial infection, BK virus enters in a latent phase in the possibly peripheral blood mononuclear cells and urogenital tract tonsils, and other hematopoietic tissues (Randhawa and Ramos, 2007). Reactivation of latent virus take place in old age, pregnancy, diabetes mellitus, acquired immunodeficiency syndrome (AIDS), congenital immunodeficiency and most importantly, organ transplantation. The initial sings of reactivation is BK polyoma viruria, which has described in 15-60 % of kidney transplant patients. These is followed by BK virus nephropathy (BKVN) and BK viremia seen sequentially in 5-30% and 1-10% of kidney transplant patients. BK polyomavirus nephropathy presents in patients with renal disease, which may be confused with acute rejection. The rate of graft loss was more than 50% in the 1990's, but has

reduced to as low as 15% because of the regular screening, and proactive reduction of immunosuppression. The first description about the BK virus nephropathy was from adult patients with kidney transplantation, but it now clear that children can also be affected by BK virus (Alexerder et al., 2006; Haysom et al., 2004; Herman et al., 2004). Additionally, cases have now been recorded after bone marrow, pancreas, liver, heart, lung, and, kidney-pancreas transplantation (Barber et al., 2006; Barton et al., 2006; Gupta et al., 2006). In addition to renal parenchymal involvement, BK virus has been connected with ureteric stricture (Gardner et al., 1971).

In patients which has bone marrow transplantation, haemorrhagic cystitis is an important clinical syndrome attributed to BK virus infection, specially after chemotherapy and radiation with urinary bladder injury have been excluded (Elidemir et al., 2007). The latter occur very early after transplantation whereas viral infection has a after onset. Milder forms of BK polyomavirus haemorrhagic cystitis are self-limited, but 5-10% of cases may encounter severe bleeding that can needs along time hospitalization. Disease outside of the urogenital tract coupled with BK virus has only rarely been occurs in the form of myopathy in kidney transplantation. A case of BK virus associated colonic ulceration has been determined (Masutanu et al., 2013). Diagnosis was not confirmed by DNA sequencing and depends on immunohistochemistry. Normally, clinical demonstration of BK virus infection that have not always been rigorously documented include salivary gland disease, oral ulcers, acute respiratory infection, meningo-encephalitis, pneumonia with viral cytopathic effect, hemophagocytic syndrome, neutropenia, bone marrow aplasia, systemic vasculopathy with capillary leakage syndrome, and paediatrics skin eruptions (Gupta, 2006).

Risk factors for BKV nephropathy

Risk factors may be donor, receiver, transplant, or virus interconnected (Bohl et al., 2008). Reported donor-related influence include deceased-donor, living-donor transplants, cytomegalovirus infection, ABO incompatibility, donor seropositive status, and donor viruria (Vera-Sempere et al., 2006). Receiver-related risk factors that have been implicate in increased for nephropathy contain older age, male gender, Asian ethnicity (Knight et al., 2013), African American race (Theodropoulos et al., 2013), Caucasian race, haemodialysis (Mitterhoffer et al., 2012), prior renal tubular injury, lower frequency of the activating natural killer cell receptor KIR3DS1 (Tridzenskaya et al., 2013), diabetes mellitus and recipient serostatus (Sood et al., 2013). Potential risk factors

connected with the transplantation method are pre-transplant desensitization (Gabardi et al., 2013), ischemic/harvesting injury, ureteric stenting, tacrolimus trough levels, delayed graft function, calcineurin inhibitor based therapy, choice of mycophenolic acid over everolimus, intensity of immunosuppression, mycophenolic acid area under the curve (AUC), multiple episodes of acute rejection, and administration of lymphocyte depleting factors (Borni-dval et al., 2013; Moscarelli et al., 2013). The effect of HLA matching is multiplex: while the risk of nephropathy is high in mismatched patients, the occurrence of graft loss is said to lower in matched patients (Awadalla et al., 2004). HLA-A2, HLA-DR15 and HLAB44 appear to lower the risk of BK polyoma viremia (Masutani et al., 2013).

Potential viral-interconnected factors include respectively alterations in the VP-1 gene, rearrangements in the NCCR region, presence of viridian in pre-transplant or day 1-5 post-transplant samples, higher viral load and quick doubling of viral copy numbers. None of the listed risk factors continuation come out statistically important in all studies. This may be due to the overriding effect of the type and intense of immunosuppression, which is further the most modifiable factor in clinical practice (Brennan et al., 2005).

Pathogenesis

Tissue injury in polyomavirus infection is believe to the result of lytic viral replication that results in cell death. It is proof that

conversion from latent to lytic viral infection is trigger by ischemic, drug induced, or refusal connected injury. The fact that the allograft kidney is prone to both ischemia and refusal may widely explain why most cases of BK polyoma virus nephropathy take place after renal transplantation, and only following rarely conditions like liver, lung, heart and bone marrow transplantation. Expression of PR inflammatory cytokines and chemokines is moderate by activation of innate protect mechanism such as the Toll-like receptor 3 pathway (Ribeiro et al., 2012). Using DNA microarray analysis of allograft kidney biopsies. It has been shown that BK polyoma virus nephropathy is connected with up-regulation of various main groups of mRNA's, including, Interferon-gamma, CXCR3, performing, CD8 and genes involved in cell cycle maintenance, apoptosis, and antiviral immunity (Abend et al., 2010). It is not able that various of these molecules are also up regulated in acute cellular rejection, and this explains why the differential diagnosis between viral nephropathy and acute rejection is a vexing problem (Randhawa and Shapiro, 2004). BK polyoma virus infection also results in the up-regulation of molecules connected with graft fibrosis, including matrix collagens, MMP9, TGF- β , MMP2, MMP9, and markers of epithelial-mesenchymal modification. Thus, continuously BK polyoma virus nephropathy can develop to chronic allograft nephropathy.

Figure 3. Replication of Polyomaviruse (Perez et al., 2006)

Replication of viruses

Transcription of Early Genes

Early gene expression is responsible for the synthesis of non structural proteins. The role of the non structural proteins is to regulate the cellular mechanisms and gene expression. Close to the N terminal end of Polyomavirus genome are enhancer elements which initiate activation and transcription of molecule called as the antigen-T. Early mRNA's encoding antigen-T are produced by host mRNA polymerase-II. T-antigen autoregulation early mRNA's. Sequentially leading to elevated levels of T-antigen. At high concentration of LT-antigen, triggering the late phase of viral infection to begin (Figure 3).

Replication of DNA genome in the nucleus

Genome replication acts to separate the early and late phase gene expression. The duplicated viral synthesized and processed as if it were cellular DNA. As the daughter viral genome is synthesized they associated with cellular nucleosomes to form structures that are often referred 'minichromosome'. In this manner the DNA packaged more efficiently (Figure4).

Transcription of late genes encoding for structural proteins (VP1, VP2 and VP3)

Late gene expression synthesizes the structural proteins, responsible for the viral particle composition. This occurs during and after genome replication. Late gene expression generated an array of proteins as a result of alternative splicing.

Group of new virions in the nucleus

In each viral protein are 'nuclear localisation signals' which cause the viral proteins to amass in the nucleus. Group of new virus particle simultaneously occurs within the nucleus of the host cell (Perez et al., 2006).

Virions are released by lysis of the cell

Release of newly synthesized Polyomavirus particle exit the

infected cell by one of two mechanisms. Firstly and less commonly, they are transported in cytoplasmic vacuoles to the plasma membrane, where budding occurs. More frequently, they are released when the cell lyses due to the cytotoxicity of virus particles present in the infected cell.

Conclusion

The name of the family Polyomaviridae, obtained from the observation that cells infected with murine polyomavirus persuade multiple (poly) tumors (omas) in immune compromised mice. Although, current evidence only supports the role of MCPyV as a carcinogen to humans. In the present review we present a summarized discussion on the current knowledge regarding the role of MCPyV, TSPyV, JCPyV and BKPyV in human cancers.

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Figure 4. Polyomaviruses replication (Perez et al., 2006)

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