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Human polyomaviruses in disease and cancer

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ABSTRACT

Today the human polyomavirus (HPyV) family consists of 10 members, BK virus (BKV) and JC virus (JCV) isolated 40 years ago and the more recently identified KI virus (KIPyV), WU virus (WUPyV), Merkel cell polyomavirus (MCPyV), HPyV6, HPyV7, trichodysplasia spinulosa virus (TSPyV), HPyV9 and MWPyV. Serological studies suggest that HPyVs subclinically infect the general population with rates ranging from 35% to 90%. However, significant disease is only observed in patients with impaired immune functions. Thus, BKV has been linked to hemorrhagic cystitis (HC) after allogeneic hematopoietic stem cell transplantation and PyV-associated nephropathy (PyVAN) after kidney transplantation; JCV to progressive multifocal leukoencephalopathy (PML) in HIV-AIDS, hematological diseases and in autoimmune diseases treated with certain lymphocyte-specific antibodies. KIPyV and WUPyV have been found in the respiratory tract, HPyV6 and 7 in the skin, and HPyV9 in serum and skin, and MWPyV in stools and skin, but so far none of these PyVs have been linked to any disease. TSPyV, on the other hand, was identified in trichodysplasia spinulosa, a rare skin disease characterized by virus-induced lytic as well as proliferative tumor-like features that is observed in immune-suppressed transplant patients. In contrast to all the other HPyVs so far, MCPyV is unique in its association with a cancer, Merkel cell carcinoma, which is a rare skin cancer arising in the elderly and chronically immunosuppressed individuals. The discovery of the new HPyVs has revived interest in the *Polyomaviridae* and their association to human disease and cancer. In this review, we summarize knowledge about this expanding family of human pathogens.

Introduction to human polyomaviruses

Polyomavirus (PyV) infections were accidentally discovered in the 1950s when characterizing a transmissible agent causing multiple tumors in rodents, hence providing the name (Greek poly- many, multiple; -oma, tumors). Gross (1953) described that filterable extracts from a mouse leukemia inoculated into newborn mice could induce tumors in the parotid gland, and the transforming entity was called the "parotid agent". Stewart and Eddy later showed that the "parotid agent" was indeed a virus that could be passaged in tissue culture (Stewart et al., 1958). It soon became clear that this murine PyV (MPyV) was ubiquitous in mice, but that tumors only developed in new-born or immunosuppressed mice (Dalianis, 2012; Ramqvist and Dalianis, 2009). In 1960, the first primate PyV was identified in African green monkey kidney cells used for the production of polio- and adenovirus vaccine. This agent was called simian virus 40 (SV40) (Sweet and Hilleman, 1960). Similar to MPyV, SV40 was shown to be oncogenic in mice and rodents leading to the concern that SV40 could also induce tumors in humans following the distribution of SV40-contaminated vaccines to almost 100 million individuals by the early 1960s.

Since then, PyVs have been detected in many vertebrate hosts including birds, rodents, cattle, and humans (Johne et al., 2011; Krumbholz et al., 2009). Despite being abundant with a highly conserved structural organization, PyVs have a narrow host and cell specificity, which appears to involve restriction on at least two levels: extracellularly via the presence or absence of receptors to invade the host cell, and intracellularly via the presence or absence of host cell factors permitting coordinated viral gene expression and completion of the viral life cycle (Atkin et al., 2009; Cheng et al., 2009). Experimentally, the restricted host and cell specificity can be overcome, and thereby, the risk of oncogenic transformation is increased, typically at the expense of lytic replication. Oncogenic transformation is mediated by the PyV early gene proteins called T (for tumor)-antigens. Key to transformation by PyVs is the genetic or functional uncoupling of T-antigen expression from the later steps of the viral life cycle consisting of viral DNA replication, late gene expression, virion assembly and eventually host cell lysis. Consequent to this

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uncoupling, cells are left with the T-antigens subverting cell cycle control by inactivating signal transduction pathways and tumor suppressors proteins *pRB* and *p53* en route to neoplastic transformation. These concepts have emerged from paradigmatic research on MPyV and SV40 as DNA tumor viruses (Cheng et al., 2009). PyVs share several features with papillomaviruses including an oncogenic potential, yet are no longer classified together as *papova*, but as the separate genus *polyomavirus* in the *polyomaviridae* family (Hirsch, 2010).

The first two human polyomaviruses (HPyVs) BK virus (BKV), and JC virus (JCV), were named after the initials of the patients from whom they were first isolated in 1971 (Gardner et al., 1971; Padgett et al., 1971). From 2007, eight more HPyVs have been identified. The third and fourth HPyVs, KI polyomavirus (KIPyVV) and WU polyomavirus (WUPyV), were named after the respective institutions e.g. Karolinska Institute (Stockholm, Sweden) (Allander et al., 2007) and Washington University (St. Louis, USA) (Gaynor et al., 2007). The fifth HPyV, MC polyomavirus (MCPyV), was named due to its detection in Merkel cell carcinoma (Feng et al., 2008). Likewise, the eight HPyV, TS polyomavirus (TSPyV), was also named according to its identification in trichodysplasia spinulosa, a rare skin disease (van der Meijden et al., 2010). HPyV6 and HPyV7, identified in skin and HPyV9 detected in serum and skin are named in order of appearance, while the tenth HPyV MWPyV found in stools and skin was named according to the first geographical location where it was found (Schowalter et al., 2010; Scuda et al., 2011; Foulongne et al., 2012; Siebrasse et al., 2012; Buck et al., 2012; Yu et al., 2012). A recent phylogenetic analysis performed for all HPyVs and other PyVs by Siebrasse et al. (2012) is presented in Fig. 1. A summary of HPyV seroprevalence in adults is presented in Table 1. Given the increasing numbers of HPyVs, the interest in their role in disease and cancer has been revived.

Polyomavirus morphology and genome structure

PyVs share a common morphology and structural organization (Cheng et al., 2009). The virions are small non-enveloped icosahedral particles of 40–45 nm diameter, with a circular double-stranded DNA genome of ~5 kb wrapped around host cell-derived histones. The particles are stable enduring high temperatures with little loss of infectivity (Brodsky et al., 1959). PyV genomes can be divided into different functional parts as demonstrated in Fig. 2.

- The non-coding control region (NCCR) harbors the origin of replication, the transcription start sites as well as promoter/enhancer elements with a multitude of seemingly redundant consensus sequences for DNA binding proteins and transcription factors. The NCCR regulates the expression of the viral early and late genes in concert with the activation and differentiation state of the host cell.
- The early gene region encodes the large T-antigen (LTag) and the small T-antigen (sTag), which are generated from one major transcript by alternative splicing. LTag and sTag facilitate viral genome replication and transformation by e.g. abrogating cell cycle control. MPyV and hamster PyVs also encode a third viral early protein called middle T-antigen (mTag), which shares splice sites with LTag and sTag, and which also contributes to cell transformation.

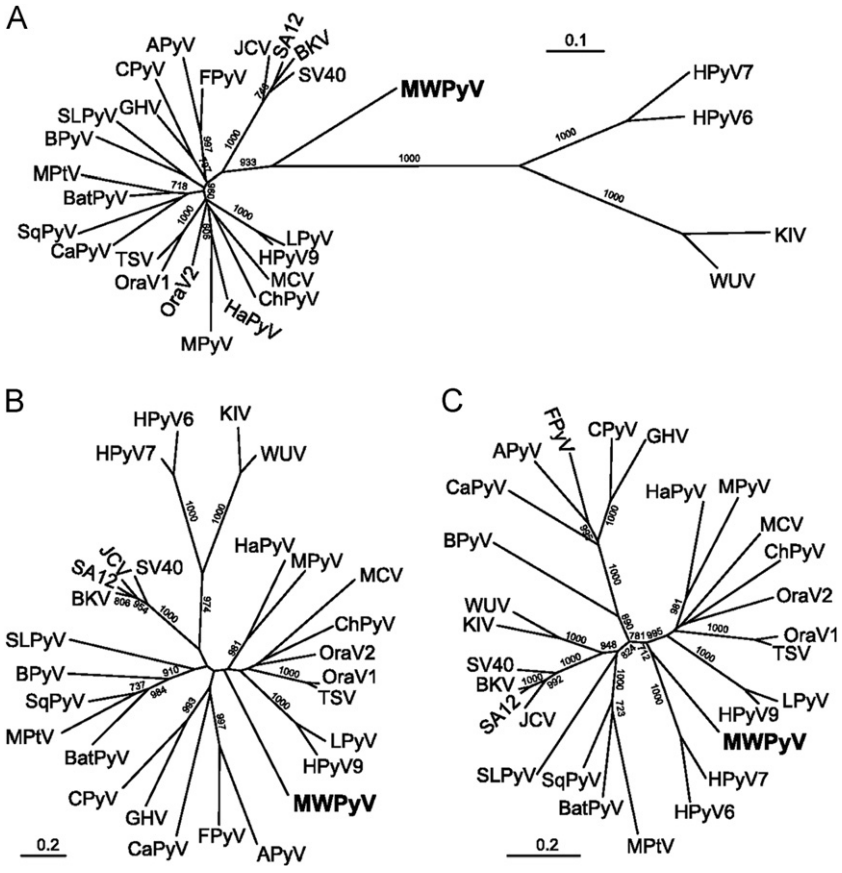

Fig. 1. Phylogenetic analysis of PyVs especially for MWPyV reprinted from Siebrasse et al. (2012), with permission from the publisher. Amino acid based trees were generated using the maximum likelihood method with 1000 bootstrap replicates. Bootstrap values less than 700 are not shown. (A) VP1; (B) VP2; (C) LTAg.