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Review

Genome analysis of non-human primate polyomaviruses

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ABSTRACT

Polyomaviruses have so far only been isolated from mammals and birds. Typical for all members of this family is their double-stranded genome of approximately 5000 base-pairs which can be divided into an early region encoding at least two functional proteins, the large and small tumor antigens, and a late region encompassing genes for the capsid proteins VP1 and VP2. During the last 10 years several novel polyomaviruses have been described in non-human primates and man. This review compares the non-human primate polyomavirus genomes that have been completely sequenced with each other and with the genomes of human polyomaviruses. We predict the presence of protein- and microRNA-encoding sequences. Our analyses demonstrate that several genetically distinct groups of non-human primate polyomaviruses exist, that different polyomaviruses can infect the same non-human primate species but that most of their proteins display highly similar domains and motifs, indicating conservation of key functions.

Contents

1. Introduction

Polyomaviruses were among the first DNA tumor viruses to be identified (Gross, 1953). The discovery of simian vacuolating agent 40 (SV40), the first polyomavirus of non-human primates (NHP) dates back to 1960; it was isolated from rhesus monkey kidney cell lines being used since the late 1950s to produce polio vaccines (Sweet and Hilleman, 1960). The oncogenic potential of

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polyomaviruses depends predominantly on one of its proteins, the large T antigen (LT-ag). This viral protein interacts with tumor suppressor proteins in the cell to interfere with the cell cycle thereby enabling viral replication and transformation of cultured rodent cells (Portolani and Borgatti, 1978; Purchio and Fareed, 1979; Topalis et al., 2013). Inoculation of polyomaviruses into laboratory rodents caused tumor formation (Cicala et al., 1993; Girardi et al., 1962; Gross, 1953). Therefore, vaccine contaminations with SV40 raised serious concerns about SV40-related tumors in humans, and SV40 has been associated with the occurrence of mesotheliomas, brain tumors and osteosarcomas. However, the respective study results could not be convincingly repeated (Shah, 2007). Since the discovery of the first human polyomaviruses, BK polyomavirus (BKPyV) and JC polyomavirus (JCPyV), in 1971 (Gardner et al., 1971; Padgett et al., 1971), 10 additional human polyomaviruses (and their variants) have been identified (Ehlers and Wieland, 2013). One of them, the Merkel cell polyomavirus (MCPyV) was shown by several research groups to be associated with the Merkel cell carcinoma, a rare but aggressive neuroendocrine tumor. MCPyV is therefore the first *bona fide* human polyomavirus that causes cancer in man (Coursaget et al., 2013).

Since it was recognized that polyomaviruses can induce tumors in foreign hosts, and since the inadvertent inoculation of the monkey virus SV40 into millions of humans, polyomaviruses of NHP became of interest. NHP are our closest relatives and exhibit a weaker genetic barrier for zoonotic virus transmission to humans than other mammals (Parrish et al., 2008). Therefore, NHP polyomaviruses may exhibit a potential for horizontal transmission to humans.

Genetically closely related polyomaviruses can serologically cross-react. This has been repeatedly observed between the closely related SV40 and BKPyV (Kean et al., 2009; Viscidi et al., 2003). NHP polyomaviruses can therefore serve as serological sentinels for the existence of so far unknown human polyomaviruses. This was first demonstrated by the discovery of a polyomavirus in cells of African green monkeys (zur Hausen and Gissmann, 1979), named Lymphotropic polyomavirus (LPyV), and the subsequent detection of neutralizing antibodies against LPyV in humans (Takemoto and Segawa, 1983). Human sero-reactivity against LPyV was also observed in more recent studies of other groups (Kean et al., 2009; Pastrana et al., 2009; Viscidi et al., 2011), and it was hypothesized that either LPyV infects humans or that a closely related polyomavirus circulates in humans that serologically cross-reacts with LPyV (Brade et al., 1981). Strikingly, such virus was discovered about 30 years later. Two groups independently identified Human Polyomavirus 9 (HPyV9) and showed that HPyV9 is genetically closely related to LPyV (Sauvage et al., 2011; Scuda et al., 2011). Subsequently, serological cross-reactivity of HPyV9 and LPyV was shown (Trusch et al., 2012). Thus, the existence of HPyV9 was indicated by a sentinel, a monkey virus, 30 years before its discovery. In line with this, the detection of human antibodies against several novel polyomaviruses from chimpanzees was taken as evidence for the existence of related, yet unknown human viruses (Scuda et al., 2013).

Since the discovery of SV40, NHP polyomaviruses (and their variants) have been identified in great apes and monkeys, and their genomes have been fully sequenced. In this review, we compare their regulatory elements, their gene content and the proteins they encode, also with those of the human polyomaviruses. Finally, we discuss the indicative potential of NHP polyomaviruses for related, yet unknown human polyomaviruses and the need for intensified identification of PyVs in non-primate mammals to achieve a proper assessment of distribution of PyV lineages.

2. Discovery, gene content and phylogeny of NHP polyomaviruses

With the exception of SV40 (Sweet and Hilleman, 1960), LPyV (Takemoto et al., 1982; zur Hausen and Gissmann, 1979) and the simian agent 12 (SA12) (Malherbe and Harwin, 1963), all fully sequenced NHP polyomaviruses have been discovered in this century, between 2005 and 2013 (Deuzing et al., 2010; Groenewoud et al., 2010; Johne et al., 2005; Verschoor et al., 2008), the majority of them from NHP living in the wild (Leendertz et al., 2011; Scuda et al., 2013; Yamaguchi et al., 2013) (Fig. 1). All complete genomes available in GenBank were included in this review that displayed a sequence similarity of less than 99% to their closest relative. For SV40, 38 genomes were available representing 2 genetically distinct groups. Therefore, from each group 1 genome (SV40 reference genome and strain SV40-RI257 genome) was included here. The final collection comprised 31 genomes, 14 from 3 great ape species, 13 from 8 old world monkey (OWM) species, and 4 from 3 new world monkey (NWM) species (Cantalupo et al., 2005; Deuzing et al., 2010; Fagrouch et al., 2011; Fiers et al., 1978; Furuno et al., 1986; Groenewoud et al., 2010; Pawlita et al., 1985; Scuda et al., 2011, 2013; Verschoor et al., 2008; Yamaguchi et al., 2013). They are listed with their hosts, accession numbers and general

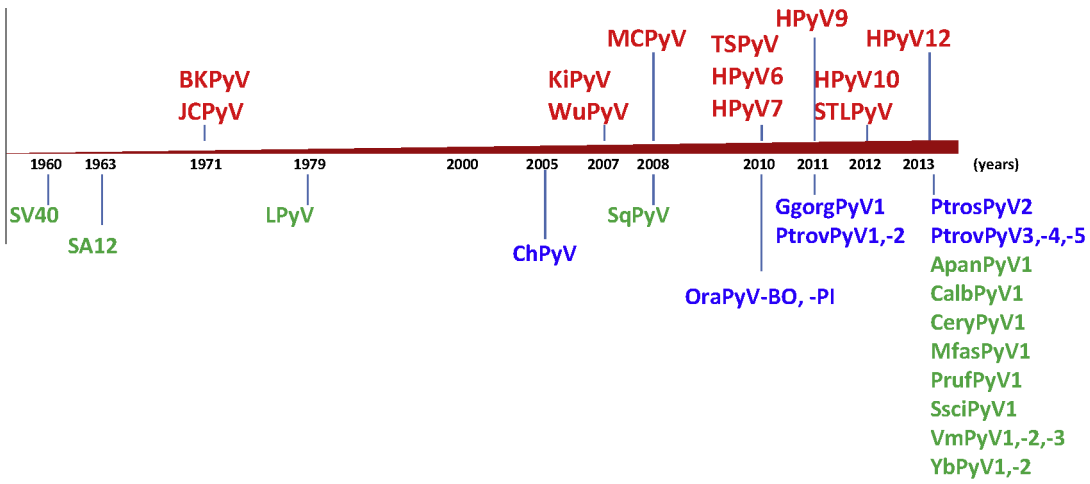

Fig. 1. Timeline of primate polyomavirus discovery. The human polyomaviruses are depicted above the time axis, while the non-human primate polyomaviruses are shown beneath. Viruses isolated from humans are given in red, those from great apes in blue and those from old world and new world monkeys in green. For abbreviations of virus names see Table 1. The time axis is not to scale. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)