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Review

Biology, evolution, and medical importance of polyomaviruses: An update

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ABSTRACT

The family *Polyomaviridae* encompasses non-enveloped viruses with a circular dsDNA genome that is typically approximately 5000 bp in length. Originally isolated from mammals, polyomavirus sequences have now been detected in invertebrates, fish, amphibians, reptiles and birds, although it remains to be determined whether all these animals are genuine hosts. The genomes of all polyomaviruses encode at least two regulatory proteins (large and small tumour antigen) and two structural proteins (capsid proteins VP1 and VP2) whose functions have been defined. The large and small tumour antigens have domains conserved among the polyomaviruses, which are responsible for specific interactions with cellular proteins and may result in alteration of the cell cycle. Additional open reading frames (ORFs) are present in the genomes of the different polyomavirus species. Some of these ORFs are transcribed and translated in viral proteins, but their functions remain poorly understood. Polyomaviruses have a restricted host specificity. This may indicate that co-divergence with their hosts, which has been demonstrated in a few cases, was an important factor during polyomavirus diversification. However, a strict co-divergence scenario fails to explain family-wide patterns of diversity, suggesting an important contribution of lineage duplication and, possibly to a lesser extent, recombination and cross-species transmission. Polyomaviruses are pathogens that can cause various malignant and non-malignant diseases in birds and mammals, including humans, but so far they have not been linked to disease in lower vertebrates. In immunosuppressed individuals, reactivation of polyomavirus BK or JC can cause serious disease of the urogenital tract and brain, respectively, while Merkel cell polyomavirus is most probably associated with the development of a highly aggressive neuroendocrine skin tumour in elderly or patients with pre-existing conditions. This review provides an update on the life cycle, prevalence, disease association, and evolution of the viruses belonging to this family.

Contents

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1. Introduction

Polyomaviruses are non-enveloped viruses with small dsDNA genomes. Of the approximately 100 polyomaviruses currently known, 80 have been recently classified as species. Based on the relationship of their viral protein large tumour antigen (LTAg), these species were assigned to four genera (*Alpha-* to *Deltapolyomavirus*) (https://talk.ictvonline.org/) (Calvignac-Spencer et al., 2016). Polyomaviruses owe their name to the ability of the first isolated member of this family to induce multiple (*poly*) tumours (*oma*) when injected into animal models (Gross, 1953); for a historical review see (Morgan, 2014). Some six decades later, fragments or complete polyomavirus genomes have been detected in diverse materials obtained from mammals, birds, reptiles, amphibians, fish and invertebrates (Buck et al., 2016; Calvignac-Spencer et al., 2016). The fast increase in identification of novel polyomaviruses is mainly due to advanced techniques such as polymerase chain reaction with degenerated primers, rolling circle amplification, and next generation sequencing. This facilitated their discovery in many different hosts and revealed several drivers of polyomavirus evolution, including co-diverging with their hosts, host-switching, lineage duplication (within the same host species), and recombination. However, discerning the relative contribution of each of these evolutionary factors during polyomavirus evolution is hampered by our biased virus sampling. While polyomaviruses of birds can cause severe diseases and even death in their host, less is known about the pathogenicity of the other polyomaviruses. Human polyomaviruses seem to be quite harmless in immunocompetent individuals, but can induce several diseases in immunocompromised patients. BK polyomavirus (BKPyV) can cause renal failure in kidney transplant patients, JC polyomavirus (JCPyV) triggers progressive multifocal leukoencephalopathy (PML) in AIDS patients and in individuals with autoimmune or haematological diseases under immunomodulatory therapy, and Trichodysplasia spinulosa polyomavirus (TSPyV) is associated with trichodysplasia spinulosa, a rare cutaneous condition in immunocompromised patients (Dalianis and Hirsch, 2013). Despite their name, so far only two polyomaviruses appear to be associated with cancer in their natural host. The human Merkel cell polyomavirus (MCPyV) is an etiological agent of Merkel cell carcinoma, an aggressive type of skin cancer caused by transformation of neuroendocrine cells of the skin, and raccoon polyomavirus (RacPyV) is associated with brain tumours (Dela Cruz et al., 2013; Feng et al., 2008). Other polyomaviruses have been suggested to be involved in human cancer development, but evidence is mostly low. BKPyV and JCPyV have been proposed to be involved in prostate cancer and colon cancer, respectively (Delbue et al., 2014; Keller et al., 2015; Niv et al., 2005; Ramamoorthy et al., 2011).

This review provides an update on the life cycle, prevalence, disease association, and evolution of the viruses belonging to this family. Included are 99 viruses that display the typical early-late architecture of polyomaviruses. Of these, 80 have been classified as distinct species according to the rules of the International Committee on Taxonomy of Viruses (ICTV) ((Calvignac-Spencer et al., 2016); http://www.ictvonline.org/virusTaxonomy.asp). In addition, 19 polyomaviruses are included that have not yet expanded into the classification process (Supplementary Table S1).

2. Molecular biology of polyomaviruses

2.1. The viral genome

Mature polyomavirus particles are built up of an icosahedral capsid, enclosing a single copy of the viral genome, which is a circular dsDNA molecule with nucleosome structure. All polyomaviruses display a similar genome organization consisting of three functional regions (Fig. 1). The early region, so called because it is expressed early in infection stage, and the late region, encoding the genes expressed after the onset of DNA replication, are separated by a non-coding control region (NCCR) (DeCaprio and Garcea, 2013). The NCCR contains the origin of replication and the regulatory sequences for early and late transcription