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Review

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Author for correspondence:
James A. DeCaprio
e-mail: james_decaprio@dfci.harvard.edu

Merkel cell polyomavirus and Merkel cell carcinoma

James A. DeCaprio[1,2]

[1]Department of Medical Oncology, Dana-Farber Cancer Institute, and [2]Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, 450 Brookline Avenue, Boston, MA 02215, USA

JAD, 0000-0002-0896-167X

Merkel cell polyomavirus (MCPyV) causes the highly aggressive and relatively rare skin cancer known as Merkel cell carcinoma (MCC). MCPyV also causes a lifelong yet relatively innocuous infection and is one of 14 distinct human polyomaviruses species. Although polyomaviruses typically do not cause illness in healthy individuals, several can cause catastrophic diseases in immunocompromised hosts. MCPyV is the only polyomavirus clearly associated with human cancer. How MCPyV causes MCC and what oncogenic events must transpire to enable this virus to cause MCC is the focus of this essay.

This article is part of the themed issue 'Human oncogenic viruses'.

1. Introduction

(a) Common infection and a rare cancer

Perhaps the most striking feature about Merkel cell polyomavirus (MCPyV) is how frequently it causes a lifelong though relatively innocuous infection yet how rarely it causes the highly aggressive skin cancer known as Merkel cell carcinoma (MCC). When MCPyV was first identified in MCC tumour specimens in 2008, it was only the fifth human polyomavirus to be identified at that time [1]. Its discovery quickly led to the realization that although MCPyV was likely to be causal in MCC, it was a typical polyomavirus, infecting most people at an early age. What has come into sharper focus is that although some of the now 14 human polyomaviruses can cause exceptionally catastrophic diseases, MCPyV is the only one clearly associated with cancer. Indeed, MCPyV has been classified by the World Health Organization-International Agency for Research on Cancer as probably carcinogenic to humans (Group 2A) [2]. How MCPyV causes MCC and what oncogenic events must transpire to enable this virus to cause MCC is the focus of this essay.

A pathogenic cause for MCC was first suspected when it was reported that the incidence of MCC was greater than 10-fold in HIV-1 AIDS patients compared with the general population [3]. In addition, the risk for developing MCC is increased in patients with medically induced immunosuppression for autoimmune conditions such as rheumatoid arthritis and solid organ transplantation [4–6]. Given the increased risk by immunosuppression for developing MCC, Huichen Feng and Masahiro Shuda in the laboratory of Yuan Chang and Patrick Moore began a search for a pathogenic cause for MCC. They performed whole transcriptome sequencing of several MCC tumours and searched for pathogens by first subtracting all human genes from their analysis. In the remaining sequences, novel transcripts distantly related to polyomaviruses were detected in a MCC tumour. Complete sequencing of the viral genome led to the determination that it corresponded to a new human polyomavirus [1]. They determined that MCPyV DNA was clonally integrated into the genome of MCC tumour cells when they observed an identical Southern blot integration pattern for a primary tumour and a metastatic lymph node from the same patient. They detected MCPyV by PCR and Southern blotting in eight of 10 tested MCC tumours, indicating that most but not all MCC contained MCPyV. These results supported the model

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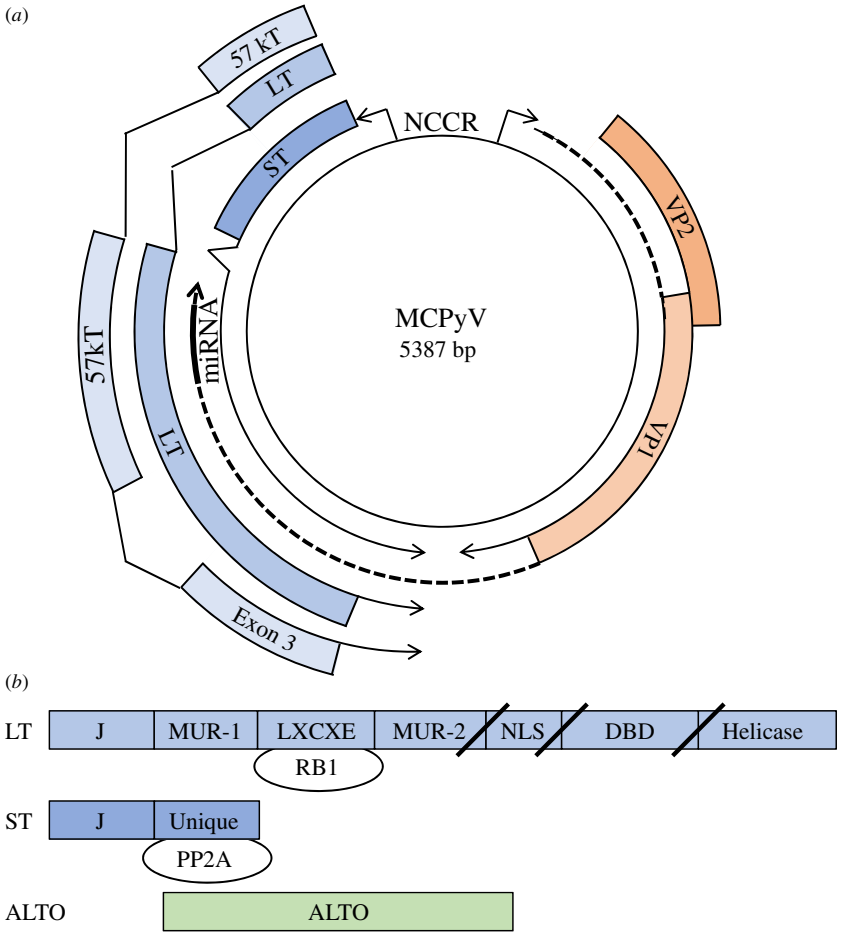

Figure 1. (*a*) Circular map of MCPyV includes early region genes for LT, ST and 57 kT and late region for VP1, VP2 and miRNA. The non-coding control region (NCCR) contains a bidirectional promoter and the viral *origin* of replication. Exon 3 of 57 kT is depicted and is in the same reading frame as LT. ALTO is not depicted. (*b*) Linear maps of LT, ST and ALTO. LT and ST share an N-terminal DNAJ or J domain. LT also contains the LXCXE or RB-binding motif, MCPyV-unique region (MUR) -1 and -2, nuclear localization signal (NLS), DNA-binding domain (DBD) and helicase domain. In MCC, mutations in LT result in truncations after the LXCXE, NLS or DBD and depicted by slashes. ST contains a unique region not shared with LT that binds to protein phosphatase 2A (PP2A). ALTO is expressed in an alternative reading frame from LT.

that MCPyV contributed to MCC in a manner similar to human papillomavirus (HPV) in cervical cancer [7].

MCPyV is a typical mammalian polyomavirus with a small (5386 bp) circular double-stranded DNA genome (figure 1*a*) [8]. There are two transcriptional units with an early region that yields four spliced mRNAs encoding four proteins including large T-antigen (LT), 57 kT, small T-antigen (ST) and ALTO (alternate frame of the large T open reading frame) and a late region encoding two viral coat proteins, VP1 and VP2, and a microRNA that targets the T-antigen transcripts [9–12]. Although the late region of MCPyV does not encode VP3, a third viral coat protein that uses an internal translation start site within VP2, most other polyomaviruses encode a VP3 [13]. The non-coding control region (NCCR) contains distinct promoters for the early and late genes, an enhancer and the viral *origin of replication* [14]. Based on its similarity to other polyomaviruses, it is likely that MCPyV LT forms two hexamers that bind in head-to-head fashion to the *origin* and serves to melt, twist and unwind the viral DNA and recruit cellular DNA polymerases to enable viral replication [15–18].

(b) Polyomavirus-associated diseases

MCPyV is one of 14 distinct human polyomaviruses species [8,19]. Primary infection with MCPyV does not cause any discernable signs or symptoms [20]. Polyomaviruses typically do not cause illness in healthy individuals although several viruses are associated with disease in immunocompromised hosts (table 1).

BK polyomavirus (BKPyV) virus is the cause of polyomavirus-associated nephropathy (PVAN) in renal transplant patients undergoing immune suppressive therapy to prevent rejection of their allograft kidney transplant [21]. PVAN may result from infection of the transplant recipient with a different strain of BKPyV that accompanied the transplanted kidney [32]. BKPyV can also cause haemorrhagic cystitis in haematopoietic stem cell transplant patients [33]. In addition, BKPyV has been associated with interstitial cystitis with bladder ulcerations and bladder pain syndrome [34,35]. Large-scale sequencing of 131 urothelial bladder cancers identified integrated copies of BKPyV in one tumour while another had integrated copies of HPV16 [36]. Whether BKPyV or HPV16 contributed to the oncogenesis of either tumour was not further explored.

JC polyomavirus (JCPyV) causes progressive multifocal leukoencephalopathy (PML) [22]. PML is characterized by lytic infection of oligodendrocytes and astrocytes with JCPyV that causes a variety of neurological symptoms including ataxia, paresis, dementia and blindness [37]. The incidence of PML increased during the AIDS epidemic but now is frequently associated with immune suppressive therapy for

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