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Possible association between polyomaviruses and gastrointestinal complications: a narrative review

Piruz Shadbash[1,2], Seyed Masoud Hosseini[2], Shahrzad Shoraka[2,3], Amir Ghaemi[4], Mehrdad Haghazali[5], Seyed Reza Mohebbi[3]

[1]Basic and Molecular Epidemiology of Gastrointestinal Disorders Research Center, Research Institute for Gastroenterology and Liver Diseases, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[2]Department of Microbiology and Microbial Biotechnology, Faculty of Life Sciences and Biotechnology, Shahid Beheshti University, Tehran, Iran
[3]Gastroenterology and Liver Diseases Research Center, Research Institute for Gastroenterology and Liver Diseases, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[4]Department of Virology, Pasteur Institute of Iran, Tehran, Iran
[5]Behbood Gastroenterology and Liver Diseases Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran

ABSTRACT

Polyomaviruses are a group of small, double-stranded DNA viruses that are known to be associated with the development of certain human diseases, but there is evidence that these viruses might be associated with gastrointestinal (GI) cancers. Several polyomaviruses have been identified, such as JC polyomavirus (JCPyV), BK polyomavirus (BKPyV) and recently Merkel cell polyomavirus (MCPyV). Although the direct effects of polyomaviruses on transformation of human cells and cancer development are not clearly recognized, their association with certain human diseases including GI cancers has been proposed through several molecular and epidemiological studies. For example, JCPyV and BKPyV have been linked to colorectal cancer, as there is growing evidence of finding viral genomes in cancerous tissues. Nevertheless, the major role of JCPyV, BKPyV and MCPyV in colorectal cancer progression is still under extensive investigation, and further surveys is required to establish a conclusive cause-and-effect relationship. Understanding the role of these viruses in cancer development has significant implications for diagnosis, treatment, and prevention strategies. It seems that proving a causal link between polyomaviruses and GI cancers might provide a novel path for targeted therapies or design and development of specific therapeutic vaccines. In addition, performing research on the possible link can provide insights into the underlying molecular mechanisms of carcinogenesis, potentially leading to the identification of novel biomarkers. This review focuses on polyomaviruses, in particular a recently discovered polyomavirus, MCPyV, and their possible link with human gastrointestinal disorders.

Keywords: Merkel cell polyomavirus, JC polyomavirus, BK polyomavirus, gastrointestinal cancer, Intestinal metastasis, programmed cell death protein 1, programmed cell death 1 ligand 1.

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Introduction

It is estimated that more than ten percent of all human cancers worldwide are associated with infectious agents, with viruses accounting for significant part of these cases (1, 2). Human tumor viruses include hepatitis B virus (HBV); hepatitis C virus (HCV); human T-cell lymphotropic virus (HTLV); Epstein-Barr virus (EBV); human herpesvirus

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Reprint or Correspondence: **Seyed Reza Mohebbi,** *Gastroenterology and Liver Diseases Research Center, Research Institute for Gastroenterology and Liver Diseases, Shahid Beheshti University of Medical Sciences, Tehran, Iran.*

E-mail: sr.mohebbi@sbmu.ac.ir
ORCID ID: 0000-0002-7020-7889

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8 (HHV-8); human papillomavirus (HPV) and Merkel cell polyomavirus (MCPyV or MCV), which have been identified as etiological agents of some cancers and have a clear oncogenic capacity that is currently widely accepted by the academic literature (3-5). HPV, EBV and JC polyomavirus (JCPyV or JCV) have even been shown to be potential risk factors for developing several gastrointestinal (GI) complications, such as gastric, colorectal and oesophageal cancers (6-9). Among these viruses, polyomaviruses can be carcinogens in laboratory animal models and can transform both animal and human cells in vitro (10). The association of JCV and BK polyomavirus (BKPyV or BKV) with GI cancers has been proposed in several studies, however there are still unanswered questions about the possible link between MCPyV, a recently discovered virus, with GI complications.

In January 2008, MCPyV was initially reported in Pittsburg, Pennsylvania (11). This virus was first found by digital transcriptome subtraction (12). It is thought to be the cause of Merkel cell carcinoma (MCC), a scarce but invasive skin cancer (13). In older children and adults MCV seems to be a common infection (14). Although the transmission mode of MCPyV has not been clearly determined yet, it can be detected in sewage, wastewater and environmental samples at high concentrations (15, 16), and a possible fecal-oral transmission has been also suggested for spread of this virus. It is discovered in respiratory secretions and can be found in healthy skin cells, digestive system tissues, and elsewhere (17, 18). In this review, we summarized the clinical and molecular aspects of MCPyV and MCC, for a better understanding of the relationship between MCPyV and cancer. In addition, the evidence for possible association between MCPyV and GI cancers have been presented.

MCPyV genome structure and functions

Polyomaviridae family is comprised of small, non-enveloped, and double-stranded DNA viruses. The classification of MCPyV, as a member of Polyomaviridae family, is briefly shown in Figure 1. The MCPyV is a DNA virus with 5387 base pair double-stranded genome and encodes several genome products, such as a large T antigen (LT and sT) and viral capsid proteins VP1 and VP2/3 genes. The genome structure of MCPyV has shown in Figure 2. MCPyV sT antigen transforms cells in vitro. MCPyV expresses a microRNA (miRNA), MCV-miR-M1, that regulates MCV LT expression and DNA replication, and downregulates the expression of host cell immune transcript SP100 which causes long-term infection in vitro. LT contains the J-domain (binding to heat shock proteins), retinoblastoma (RB) binding motif (inhibiting effects on RB family), and the C-terminal origin-binding and helicase/ATPase domains (needed for the replication of viral DNA). The oncogenic function of LT antigen is relevant to the high binding affinity of LT to RB (19-21). For persistent growth of MCPyV-positive MCC tumors, the RB binding of MCPyV LT is needed. MCPyV sT is the main viral oncogene involved in virus-caused cell transformation. To transform immortalized rodent fibroblasts, expression of sT alone is enough and also in vivo studies show transforming activity. sT performs this

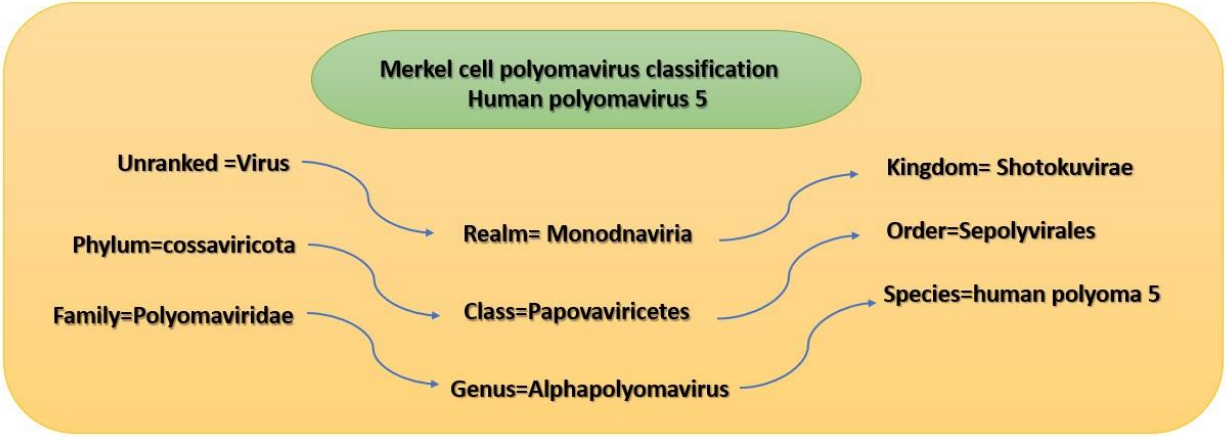


Figure 1. The classification of Merkel cell polyomavirus

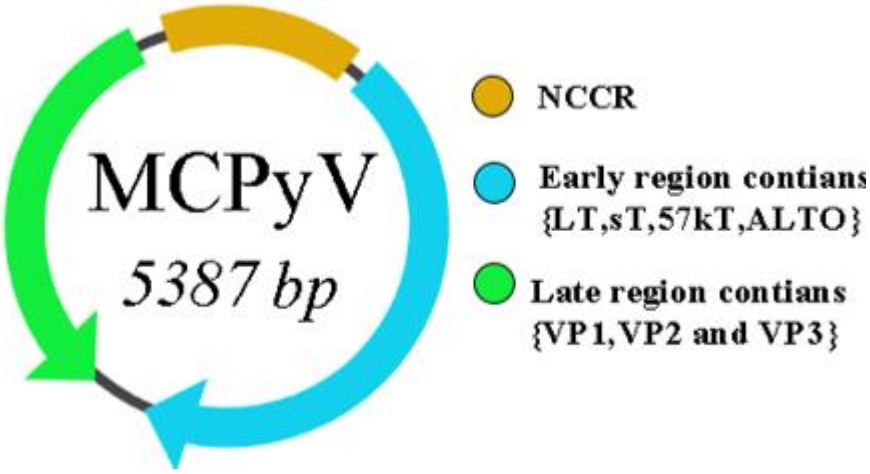


Figure 2. The genome structure of MCPyV. MCPyV genome is circular, double stranded DNA that contains a non-coding region (NCCR) an early region encoding T antigens, and a late region including the genes for the viral capsid proteins VP1, VP2, and VP3.

function by keeping the hyper-phosphorylation and inactivation condition of the eukaryotic translation initiation factor 4E-binding protein1 (4E-BP1), causing to dysregulate of cap-dependent translation that speeds up cell proliferation and malignant transformation. sT is also important for inhibiting MCPyV LT proteasomal degradation and other cell-cycle regulators including c-Myc and cyclin E targeting the cellular ubiquitin ligase SCFF bw7, helping in viral replication and host cell transformation (22-24). MCPyV genome can be detected in many MCC tumors and are often integrated into the cellular genome, leading to tumor-specific truncation variations (25, 26).

JC and BK polyomavirus

JCV and BKV are other important viruses from Polyomaviridae family. JCV is responsible for the occurrence of progressive multifocal leukoencephalopathy (PML), a disease causing demyelination of the central nervous system (27, 28). The BKV is one of the main causes of interstitial nephritis in kidney transplant recipients and haemorrhagic cystitis (29, 30). In addition, BKV is also linked to other human diseases such as ureteral stenosis, pneumonia, vascular illnesses, retinopathy, inflammation of the brain and colorectal cancer (31-33). The primary infection with BKV happens in early years of life, whereas JCV infection happens at older ages. The International Agency for Cancer Research Monograph Working Group belonging to WHO classified BKV and JCV as "probably carcinogenic to humans" (34). The existence of JCV DNA within the upper and lower parts of the human gastrointestinal tract and especially within the mucosa of the human colon and colorectal cancers has been recently described (35, 36). One study showed high levels of JCV and BKV in samples of urban sewage and the authors also indicated the relatively high stability of these viruses in sewage propose that GI track might be a vital point of transmission of these viruses among individuals (37). The high prevalence of human polyomaviruses observed in urban sewage proposes that people are being exposed at a high frequency to JCV and BKV through the digestive tract (38, 39). JCV DNA sequences are display within the GI mucosa of over 75% of immunocompetent people (70.6% of upper GI and 81.2% of colonic tests) (36). JCV T-Ag DNA sequences are regularly show in adenomatous polyps of the colon (82%) (40). In a study by Selgerd et al., it was illustrated that immunosuppressed patients have a higher prevalence of JCV T-Ag DNA in typical colonic mucosa, compared with immunocompetent controls (41). The work of Laghi et al. was the primary investigation analyzing JCV in colorectal neoplasm. Laghi et al. have proposed that JCV can be a risk factor for CRC. JCV DNA found in 89% of colorectal carcinomas (CRCs) and 89% of typical adjacent mucosa, and T-Ag was display in up to 81% of CRCs (35, 42, 43). Newcomb et al. could not found JCV sequences in more than 0.5% of paraffin-embedded CRC samples (44). Ricciardiello et al. illustrated that Mad-1 is the only JCV subtype detected within the colon (45). JCV T-Ag DNA within the ordinary GI

mucosa of immunosuppressed patients may be noteworthy that this people is at higher risk of neoplasia (46-53). Mou et al. detailed that the absolute copy numbers for JCV DNA in CRC tumors were lower than one copy per cell (54). In American patients, JCV DNA was frequently illustrated in 80% of CRC tissue samples. Casini et al. detected 89% JCV/BKV positivity in Italian CRC patients. Two studies in Asia have reported JCV positivity in 26.1% and 84.6% of CRC tissues. In an Italian study, only 50% of CRC cases had the reverse relationship between T-Ag protein and miR-J1-5p, which happens during JCV replication (55). JCV is found in 40% of typical colon mucosa, and higher prevalence of JCV (90%) has been found in colorectal cancer cases (56). Similar association has been found between infection with BKV and CRC (31). five studies had related to the prevalence of BKV in CRC patients (55). There are also studies about the presence of BKV DNA in different tumor types, e.g. neoplasms of the large intestine, pancreas, prostate, skin and brain.

Risk factors of MCC

So far, MCPyV replicates poorly in most of cell lines that have been tested. However, in a recent survey, scientists found human dermal fibroblasts as natural host cells for MCPyV infection. Risk factors of MCC, like the radiation of UV and increasing age, provoke WNT signaling and MMP expression can exacerbate MCC infection and thus cause oncogenesis (57-61).

Host immune responses to MCPyV infection and MCC

Immunosuppressed individuals are susceptible to MCC, suggesting that the host immune responses play crucial roles in MCC. Additional evidence like complete spontaneous tumor regression and tumor-reactive T cells are involved in the prevention and control of MCC (62, 63). In addition, MCC patients with strong immune responses show better prognosis and the infiltration of CD8+ and CD4+ intratumoral lymphocytes that anticipates a better survival. Nevertheless, most MCC patients have a natural basic immune response to the infection and disease progression (64-67). Tumors of MCC keep expanding despite the proliferation and activation of T cells against MCPyV capsid proteins and oncoproteins. In a study, 84% of MCC tumors displayed MHC-I downregulation, and MHC-I expression was lower in MCPyV-positive tumors than in MCPyV-negative samples (68). Another way that MCPyV escapes from the immune response is by downregulating Tolls like Receptor 9 (TLR9), one of the important host innate immune response sensors. MCPyV sT downregulates cellular gene expression related to the NF-KB pathway, which can modulate the host immune response for MCPyV infection (69, 70).

Detection of tumor-related MCPyV

Techniques for the detection of MCPyV in tumors contain immunohistochemistry, PCR, RNA or DNA in situ hybridization, and next-generation sequencing (NGS) (71-75). CM2B4 is a commercially accessible mouse monoclonal antibody for the detection of MCPyV LT and is about 88% sensitive and 94% specific (compared to multimodal methods combining PCR with immunohistochemistry. In both tonsillar and lymphoid tissues nonspecific staining with CM2B4 can be applied successfully (76, 77). Other antibodies are reported for diagnosing the LT, sT, or the common T antigen region and can be helpful in viral protein detection. In tumor samples with low purity, copy number estimation of tumor-related MCPyV can be confounded by background signals from the skin and/or tumors of non-MCC. qPCR does not allow for visual verification that results are related to tumor cells; so, background MCPyV infection cannot be excluded in tumors of MCC with low signal (45). A multimodal approach combining PCR and immunohistochemistry is more sensitive and specific for detecting MCPyV (78, 79).

Merkel cell carcinoma

In 1875 Friedrich Sigmund Merkel (1845-1919) was a German anatomist and histopathologist who first described the Tastzellen (touch cells). In 1972 Merkel cell carcinoma (MCC) was first described by Cyril Toker. MCC also known as cutaneous APUDoma, primary neuroendocrine carcinoma of the skin, and trabecular skin cancer. Factors contributing to the development of the MCC contain the Merkel cell polyomavirus (MCPyV or MCV), a weak immune system, and exposure to ultraviolet radiation (80, 81). MCC generally occurs in the head, neck, and extremities, as well as in the perianal and eyelid areas. This disease is more frequent in people above 60, Caucasians, and men. MCC is less seen in children.

MCC tumors can be painless, and itchy, and other MCC appearances as papules or plaques are diagnosed. Characteristics of MCC in 2008 summarized in the acronym AEIOU (Asymptomatic/insensitive symptoms, rapid spread, immunosuppressing over 50 years, and the location of UV exposure in a light-skinned person (38). Ninety percent of MCCs contain 3 or more of these attributes. MCC is occasionally confused with another histological kind of cancer, containing basal cell carcinoma, squamous cell carcinoma, malignant melanoma, lymphoma, and small cell carcinoma, or as a benign cyst. MCCs also diffuse via blood vessels to many organs, especially the liver, lungs, brain, and bone. The presence of MCPyV has been analyzed in various human cancers. Low viral load of MCPyV was detected in Iranian patients with head and neck squamous cell carcinoma (82). In addition, there are evidences that found MCPyV in non-small cell lung cancer (83, 84).

Cell origin of MCC

The origin of Merkel cells is suggested to be gained from neural crest cells or epidermal progenitors. In addition, the piezo 2 ion channel and the transcription factor Atoh1, which are particular for Merkel cells, are expressed by MCC. Merkel cells are post-mitotic cells that are less likely to develop cancer. In addition, they are not displayed to support Merkel cell polyomavirus infection, which leads to oncogenesis in about 80% of MCCs. Laboratory experiments showed that fibroblasts support MCV infection and can also be induced to have MCC phenotype by viral protein expressions (85-91). Epithelial cells have not normally been identified in the dermis, hair follicles contain epithelial cells that are suggested as a potential site for MCC precursor. The presence of B-cell surface markers in MCC, with a high correlation between MCC and B-cell lymphomatous cancers, also leads to suggest that MCC may share a precursor with B-cells (92-94). However, due to differences in physiology and prognosis between MCV (+) and MCV (-) MCC, some proposed that these two MCC subtypes may be derived from various progenitor cells (79). MCCs often observed in the dermis but may occur from any skin layer (from intraepidermal to subcutaneous). Merkel cells are post-mitotic and have no proliferative activity and reduce the likelihood of tumorigenic potential in them. Merkel cells are derived from the epidermis, while MCC tumors arise predominantly in the dermis and subcutis, with no obvious connection to the epidermis. It is suggested that MCC tumors may originate from pro-/pre-B cells, however, this theory is still being tested. Most tumors of MCC develop in the human dermis. MCC also expresses in genes that are generally transcribed in benign Merkel cells (87, 95-99). MCPyV actively replicates in the dermal fibroblasts placed on the border between the epidermis and dermis and may shed viral particles that inadvertently enter Merkel cells or their progenitor cells present in adjacency to the basal layer of the epidermis (32). About 80% of MCC tumors infected with MCV, in a monoclonal pattern the MCV integrated into the host genome. The relation between MCC and UV exposure, as well as among those who receive phototherapy of UV. The MCC incident rate is increased in situations with faulty immune functions, including malignancy, HIV infection, and organ transplant patients, etc. Patients with rapid immune response displayed to have better prognoses. This is thought to be due to the body's inability to defend against infection by or reactivation of MVC. The exact origin of MCC is still unclear (100-104).

Epidemiology of MCC

The MCC incident rate is approximately twice as high in men than in women. Since 2013, MCC annual rate in the USA was 0.7 cases per 100,000 persons. In the USA, the MCC incidence was nearly twice between 2000 and 2013 and is anticipated to increase by 3000 cases per year by 2025, with alike increases in Australia and many but not all European countries. In the United States since 2005, approximately 2500 novel cases of MCC are identified per year, as compared to almost 60,000 novel cases of malignant melanoma and more than 1 million novel cases of nonmelanoma skin cancer. The frequency of MCC is higher closer to the equator and lower in those of non-white races. The highest MCC incidence is in Australia but has a lower incidence of MCV-positive MCC than found in other countries. Since 2006, other primary cancers have been found to remarkably increase the risk of MCC, particularly in those with previous multiple myeloma, chronic lymphocytic leukemia, and malignant melanoma. The primary case of intra-abdominal involvement, metastasis to the colon, was detailed in 1984, with cases of

metastasis to the small intestine detailed afterward. A case of generalised metastasis to the upper gastrointestinal tract, found at dissection, has moreover been detailed in 2010, metastasis to the stomach organs was detailed in up to 17 cases, most commonly within the stomach. Immunosuppression containing HIV infection or immunosuppressive treatment following an organ transplant or for autoimmune disease can also enhance the likelihood of developing MCC. Prevalence estimates fall below zero in patients under 40 years old and 90% of patients are over 50 years old. Different from many other cancers, where disease prevalence peaks and then declines with increasing age, the incidence of MCC continues to increase even as patients reach 80 or even 90 years of age, likely due to an aging immune system (105-109). There are also reports on the presence of MCPyV in papillary thyroid cancer (85).

MCC diagnosis and prevention

MCC diagnosis starts with a clinical exam of the skin and lymph nodes. After clinical examination, the Merkel cell carcinoma (MCC) definitive diagnosis needs an examination of biopsy tissue to detect its histopathological attributes. An ideal biopsy specimen is a punch biopsy or a complete-thickness incisional biopsy of the skin containing full-thickness dermis and subcutaneous fat on light microscopy, MCC displays basaloid tumor nests with neuroendocrine attributes ("salt and pepper") chromatin, rare cytoplasm and rapid mitotic activity. American Academy of Dermatology and Skin Cancer foundation suggest some measures for stopping overexposure to UV and skin cancer (110, 111).

Management of MCC

Adjuvant radiotherapy at the location of the primary tumor is frequently suggested; therefore, the risks of radiotherapy-related complications can be eluded by a low positional relapse rate in a group of patients. The NCCN suggests imaging studies for distant metastases to manage the clinically detectable or secret nodal disease, followed by dissection of lymph nodes and/or radiation therapy to the nodal basin (112, 113).

Chemotherapy

Although some chemotherapeutic regiments displayed temporary effects, studies did not identify any remarkable long-term impact on recurrence rate or life expectancy. Since 2015, there was no FDA-approved standard chemotherapy regimen for MCC therapy. It is suggested to pay attention to chemotherapy on a case-by-case basis (90, 114).

Immunotherapy

For the treatment of patients with metastatic MCC, the anti-PD-L1 antibody avelumb has been approved by the FDA, the European Medicines Agency (EMA), Swissmedic, and the Japanese Ministry of Health, Labor and Welfare in the past 2 years. Other immunotherapies for MCC have shown effectiveness in clinical trials. The abscopal effect of radiation therapy (in which local radiotherapy is accompanied by extra tumor foci regression found outside the therapy field) has been seen in MCC patients, indicating a modulated immune response. Another signaling pathway (containing the Cytotoxic T lymphocyte antigen 4 (CTLA-4) and programmed cell death protein1 (PD-1)-PDL1 immune checkpoints repress immune responses and can be used by tumor cells as an immune evasion mechanism. So, immune therapies enhance antitumor immunity either by activating stimulatory pathways or by suppressing inhibitory pathways (115-119).

Polyomaviruses and gastrointestinal cancers

The possible link between JCPyV genome detection and certain human tumour types, including colorectal cancer and oesophageal cancer, has been investigated in several studies (35, 43, 55, 56, 120-123). It was shown that the prevalence of JCPyV in CRC tissue was 81-89%, and that the virus was mainly found in CRC sections compared to the surrounding normal tissue. Quantification of JCPyV genome revealed a significantly higher in the colon neoplasm in comparison to normal tissues (124). The hypothesis of a probable role of JCPyV TAg in CRC has been supported by further epidemiological and experimental evidence. Hori and colleagues found TAg in 26% of CRC studied samples, nevertheless, they could not detect it in normal control tissues (125). Uleri and colleagues also found an association between JCPyV and the disease, nonetheless, they proposed that the probable involvement of tumorigenesis should occur at pre-polyp stages (126).

Enam and colleagues found evidence of a possible association between JCV and colorectal cancer, suggesting a novel regulatory role for T-antigen in deregulating the Wnt pathway via β-catenin in gastrointestinal tumors (43). JCPyV is also proposed as a

risk factor for gastric carcinogenesis by several other studies. Murai and colleagues found that the gastric epithelium in most Japanese people is infected with JCV at a low level but higher levels of infection may be associated with gastric cancer development (127). Shin et al. found JCPyV T-Ag expression in human gastric cancers and suggested a possible role for this polyomavirus in gastric carcinogenesis (128). Although the oncogenic properties of MCPyV in MCC are well documented, data on the possible association between this virus and gastrointestinal cancers are insufficient and require further study. Campello et al. evaluated fresh tissue and blood samples from 64 colorectal cancer cases and 80 relatives. MCPyV could be recovered frequently from the gastrointestinal tract. MCPyV DNA was identified in 12.5% of adenoma/polyp tissue. Blood samples from both cases and controls were negative. When comparing the prevalence of Merkel cell polyomavirus in normal, pre-cancerous and cancerous tissue, no statistically significant difference was found (129). Karbalaie Niya and colleagues analyzed archived formalin-fixed, paraffin-embedded tissue samples of CRC patients in comparison with controls. Nevertheless, they found no positive samples in either CRC or controls (130).

Discussion

Polyomaviruses infections seems to be common in patients with gastrointestinal cancers and might be considered as a possible risk factor. In addition, large surveys and molecular cause and effect studies are necessary to reveal whether MCPyV, is associated with GI cancers or not. Gathering more details for linking between polyomaviruses and GI cancers might provide a new opportunity for designing targeted therapies against these viruses.

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Conflict of interests

There is no conflict of interest for authors of this article.

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