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VIRUSES OF POLYOMAVIRUS FAMILY LIKE MCV, WUV AND KIV INVOLVED IN HUMAN DISEASES

Véronique Petit[1], Konrad Rejdak[1], Janusz Kocki[2]*

[1] Department of Neurology, Medical University of Lublin, Poland
[2] Department of Clinical Genetics, Medical University of Lublin, Poland

*Corresponding author e-mail: vpetit@onet.pl

S u m m a r y. Polyomaviruses are a family of small DNA viruses known to infect a wide range of vertebrates and invertebrates. Although polyomaviruses do not typically cause illness in healthy individuals, several polyomaviruses may result in catastrophic diseases in immunocompromised hosts. The article is a review of the reports available in PubMed on selected polyomavirus, i.e. Merkel cell polyomaviruses (MCV), Washington University virus (WUV) and Karolinska Institute viruses (KIV) involved in human diseases. Besides, MCV is likely to cause Merkell cell carcinoma. The viruses like WUV and KIV are also involved in the development of respiratory tract infections.

K e y w o r d s: DNA virus, polyomaviruses, Merkell cell polyomavirus, KI virus, WU virus

INTRODUCTION

Polyomaviruses (PyVs) are a family of small DNA viruses known to infect a wide range of vertebrates and invertebrates [20]. Infections with polyomaviruses are *widespread***.** The polyomaviruses have similar genetic makeup [4]. They are nonenveloped icosahedral viruses with circular double-stranded DNA genomes of approximately 5,000 base pairs (bp) [20].

Genes of polyomaviruses encode small and large T-region proteins which play a role in viral replication and are implicated in viral chromosomal integration, as well as in possible dysregulation of growth factors gene, and viral capsid proteins VP1, VP2 and VP3 [4]. Structural capsid proteins, including VP1, VP2 and VP3 are coded by late gene region. Multiple regulatory proteins known as tumor antigens (T-Ag) are coded by early viral gene region by alternative splicing [20].

The cause of subclinical infections are 12 of the 13 known polyomaviruses detected in humans [6, 20]. Although polyomaviruses do not typically cause illness in healthy individuals, several polyomaviruses may trigger catastrophic diseases in immunosuppressed individuals, including post-transplantation and AIDS patients [6, 20].

Polyomaviruses are known to have a potential for causing severe end-organ damage or malignant transformation which may occur in patients with weakened immunity unable to mount or regain endogenous T-cell responses as a result of leukemia or iatrogenic immunosuppression in autoimmunity, bone marrow and solid organ transplant settings [5, 26].

MATERIALS, METHODS AND AIM OF THE STUDY

The work is based on the review of reports on polyomaviruses accessible from PubMed over the last 5 years. We focused on the literature about Merkel cell polyomaviruses (MCV), Washington University virus (WUV) and Karolinska Institute viruses (KIV). We discuss the role of these viruses and their potential to cause diseases.

RESULTS

MCV

MCV is a novel human polyomavirus that accounts for widespread infections affecting general population [18]. MCV is named after neoplastically altered Merkel cells where the pathogen was first discovered in 2008, which was associated with the discovery of Merkell cell carcinoma due to Merkel cell polyomavirus [2, 22, 33]. Merkell cell polyomavirus is a tumorigenic DNA virus present in most Merkell cell carcinoma (MCC) tumors [13]. The genome of MCV is very large and contains 5,387 bp [22]. MCV is clonally integrated into MCC genome and approximately 80% of MCC are MCV-positive [23]. Merkel cell carcinoma encompasses primarily cutaneous neuroendocrine carcinomas [13, 19].

MCC is a highly aggressive, relatively rare skin cancer, killing more patients than other well-known cancers such as cutaneous T-cell lymphoma or chronic myelogenous leukemia, whose incidence has tripled over the past two decades [6, 18]. Merkel cell polyomavirus-negative tumors have a high load of UV-signature mutations, much similar to melanoma [13]. Further research is needed in order to understand MCC as a potentially virally driven tumor that can be targeted with adoptively transferred T cells specific for viral oncoproteins [5]. Colombara *et al.* show that infection with MCV and human polyomaviruses (HPyVs) likely does not influence a person's risk of lung cancer, especially in Western smoking populations [2, 3]. Few MCV studies have showed prevalence estimates of up to nearly 40% for MCV DNA in lung tumors [2, 12, 14, 15, 17], however an American study reported MCV antibodies were not associated with lung cancer [3].

Shikova *et al.* believes the role of Merkell cell polyomavirus as a respiratory pathogen is controversial [24]. The study examined 221 specimens obtained from patients with acute respiratory diseases and chronic lung disease, including lung cancers, and all specimens from nonmalignant chronic lung diseases and lung cancer; they obtained MCV-negative results on nested polymerase chain reaction [24].

WUV

In 2007 Washington University research group, USA isolated a virus from the respiratory system [22]. The virus was named after the institution where it was detected. Gaynor *et al.* describe WUV as a double-stranded DNA virus with non-enveloped and icosahedral capsid, isolated from patients with acute respiratory tract infections [7, 11]. WUV infection usually occurs in early childhood [22]. The genome of WUV contains 5,229 bp [22]. It is well known that viruses are major causative agents of respiratory tract infections, thus WUV is likely to account for many respiratory tract problems [8]. Essa *et al.* found 18 (3.9%) patients who tested positively for WUV out of 459 patients hospitalized for respiratory tract infections, especially those diagnosed with bronchitis, pneumonia and bronchopneumonia in Kuwait [7]. Another study reported on 10 (3.5%) patients who were WUV-positive out of 735 hospitalized patients for respiratory tract infections, such as pneumonia, bronchiolitis, bronchopneumonia and respiratory distress in Kuwait [8]. The incidence of WUV was highest from February to March and from October to January [8]. Co-infection with other respiratory viruses was notable. Moreover, viral co-infection, especially by respiratory syncytial virus and human rhinovirus were detected in 9 patients (50%) among WUV- infected children [1]. Robaina *et al.* noticed that polyomavirus detection, especially WUV was higher among young healthy individuals under the age of 20 compared with over 50-year-olds [21].

Some studies investigated the correlation between human polyomaviruses and the incidence of lung cancer. Colombara *et al.* showed that infection with WUV is not likely to influence person's risk of lung cancer, especially in Western smoking populations [2, 3].

KIV

In 2007 in Karolinska Institute, Sweden the researchers isolated a virus from the respiratory system [22]. This virus was named KIV after the institution where it was discovered. The genome of KIV is built of 5,040 bp [22]. KIV infections were observed more commonly in persons over 50 years old [21]. The viruses like KIV were associated with the development of respiratory tract infections. KIV infection usually occurs in early childhood [22]. One of the reports found 4 (1.4%) patients were KIV-positive among 735 hospitalized patients for respiratory tract infections such pneumonia, bronchiolitis, bronchopneumonia and respiratory distress in

Kuwait [8]. The incidence of KIV was highest from February to March and from October to January [8]. Swedish researchers found KIV in nasopharyngeal aspirates (NPA), and the feces from patients with respiratory tract infections [1, 7].

Some authors report on the correlation between human polyomaviruses and the incidence of lung cancer. Colombara *et al*. show that infection with KIV and HPyVs probably does not influence person's risk of lung cancer, especially in Western smoking populations [2, 3].

Other polyomaviruses

The trichodysplasia spinulosa-associated polyomavirus (TSAPyV, TSV) is likely to cause a rare skin dysplasia, i.e. trichodysplasia spinulosa. Other polyomaviruses have not been strongly associated with this clinical disease to date [4]. The researchers also mention human polyomavirus 7 (HPyV7) [16, 20]. HPyVs may have carcinogenic potential in humans [2]. There are also known nonhuman polyomaviruses, e.g. rat polyomavirus 2 (RatPyV2). That novel polyomavirus was detected in the parotid salivary gland from a breeding colony of rats with X-linked severe combined immunodeficiency. Research shows that RatPyV2 accounts for the infection in the lung epithelium and many other respiratory, reproductive and glandular tissues of rats [20]. This 5.1-kbp polyomavirus genome is closely related to WUV and KIV.

DISCUSSION

The transmission of polyomaviruses has not been well-recognized. Polyomaviruses could be transmitted by respiratory, fecal-oral route, via blood and transplanted organs [22]. The main sites where KIV and WUV lodge are respiratory tissues, however polyomaviruses, e.g. BKV and JCV persist mainly in the urinary tract tissues [22].

Some polyomavirus act as respiratory pathogens. Viruses are major causative agents of respiratory tract infections, e.g. WUV may be responsible for many respiratory tract illnesses [8]. KIV is also involved in the development of respiratory tract infections. KIV was detected in nasopharyngeal aspirates (NPA) from patients with respiratory tract infections, however MCV role in respiratory tract infections is disputable [1, 7, 24].

Polyomaviruses are also associated with a broad spectrum of diseases, including cancers, particularly in immunosuppressed hosts [20]. Polyomaviruses could be associated with neoplastic process, but many scientific studies appear contradictory. The evidence for an association between polyomaviruses such KIV or WUV and lung cancer is not consistent [3]. Colombara *et al.* show that infection with MCV does not influence person's risk of lung cancer, especially in Western smoking populations [2, 3]. MCV is a novel human polyomavirus which is detected in most MCC tumors. But MCC encompasses primarily cutaneous neuroendocrine carcinomas [13, 19]. A recent International Agency for Research on Cancer Panel classified Merkell cell polyomavirus as a probable carcinogen [15, 27].

The relationship between polyomavirus antibodies such as BKV, JCV, MCV, TSV, WUV, KIV and HPyV7 and non-Hodgkin lymphoma (NHL) incidence was examined by fluorescent bead-based multiplex method in 279 NHL patients and 557 controls [27]. Teras *et al.* found an inverse dependence between TSV antibody levels and NHL risk. There were no other links observed between polyomaviruses and NHL risk [27]. Human polyomaviruses antibody levels do not favor a higher NHL risk in immunocompetent individuals [27]. Therefore further studies are postulated.

Although these viruses typically do not cause illness in healthy individuals, several polyomaviruses can cause catastrophic diseases in immunosuppressed individuals, including post-transplantation and AIDS patients [6, 20].

CONCLUSIONS

Antibodies specific for each of 13 human polyomaviruses have been identified in a high percentage of healthy individuals [4]. Thereby we can conclude a high rate of exposure to each of the polyomaviruses in human population. PCR methods are now well available for the detection of polyomaviruses in a variety of clinical samples [4]. WUV can cause pneumonia [25, 28]. KIV is associated with the development of respiratory tract infections. KIV and WUV can account for respiratory infections, and MCV is the cause of Merkell cell carcinoma [9, 22]. Skin dysplasia is caused by TSV [3, 20]. Prompt early identification of viral infections can help reduce implementation of antibiotics, and improve

treatment and management strategies. Other adverse events also require further studies to fully elucidate the problem.

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