EDITORIAL

For reprint orders, please contact: reprints@futuremedicine.com

Considerations on the link between Merkel cell polyomavirus and lung cancer

“In summary, detection of Merkel cell polyomavirus with a tumor-specific signature in lung cancer suggests a direct or indirect pathogenetic role of Merkel cell polyomavirus in non-small-cell lung cancer.”

Yumiko Hashida¹ & Masanori Daibata^{*1}

Smoking is well known to be a predominant risk factor for the development of lung cancer, but lung cancers occurring in never smokers has increased in recent times [1]. It is also shown that the increase in the incidence of lung cancer in never smokers is higher in east Asia than the US or European countries [1]. These findings suggest that factors other than smoking may be etiological and risk factors for lung cancer. Some environmental agents, such as radon, asbestos and cooking fumes, have also been implicated in its development [1,2]. However, to date, a large fraction of lung cancers have not been definitively associated with such environmental risk factors, highlighting the need for additional epidemiological research.

Infectious agents including oncogenic viruses have been proposed to be associated with the pathogenesis of lung cancer. Many studies suggest that human papillomavirus (HPV) is detectable in cases of lung cancer worldwide [3]. However, the prevalence rate of HPV infection in patients with lung

cancer varies across different countries. A higher incidence of HPV in lung cancers has been reported in Asian cohorts [4]. Another human tumor virus, Epstein–Barr virus, is found in lung cancers, especially in lymphoepithelioma-like carcinomas, predominantly in Asian patients [5]. Recently, the presence of murine mammary tumor virus-like sequence was identified in 18% of the lung cancer from Mexican patients [6]. Thus, the prevalence of viral infections in lung cancers appears to depend on geographic location.

In 2008, a new human tumor virus, designated Merkel cell polyomavirus (MCPyV), was reported in Merkel cell carcinoma (MCC), a neuroendocrine carcinoma of the skin [7]. Although the route of MCPyV transmission has not been established, MCPyV genome is detected in lower respiratory tract secretions [8]. It is conceivable that long-standing exposure of the respiratory tract to this oncogenic virus may lead to development of cancer in this region.

KEYWORDS

- epidemiology • lung cancer
- Merkel cell polyomavirus
- oncovirus

“Infectious agents including oncogenic viruses have been proposed to be associated with the pathogenesis of lung cancer.”

¹Department of Microbiology & Infection, Kochi Medical School, Kochi University, Nankoku, Kochi 783-8505, Japan

^{*}Author for correspondence: Tel.: +81 88 880 2321; Fax: +81 88 880 2324; daibatam@kochi-u.ac.jp

Based on the histological similarities between MCC and small-cell lung cancer (SCLC), the possible association between MCPyV and SCLC was studied at first. Two German groups showed the presence of MCPyV DNA by PCR with detection rates of 6.7% (2/30) and 38.9% (7/18) [9,10]. However, the results are discrepant among research groups in subsequent studies, and as of now it is unlikely that MCPyV plays a significant pathogenetic role in SCLC. As for non-small-cell lung cancer (NSCLC), three epidemiological studies undertaken in American and European patients detected MCPyV DNA by PCR in 16.7% (5/30), 4.7% (4/86) and 9.1% (10/110) of NSCLCs [11–13].

MCPyV DNA positivity alone is not sufficiently specific to establish its etiological role of MCPyV in lung cancer because viral DNA fragments could be detected in the lower respiratory tract when a high-sensitive PCR assay is used [8]. Several oncogenic mechanisms of MCPyV have been proposed in MCPyV-positive MCC. Expression of the MCPyV large T (LT) antigen is essential for the oncogenesis of MCPyV-positive MCC [14,15]. The MCPyV *LT* gene contains tumor-specific mutations that truncate the LT antigen and ablate viral replication capacity but preserve its oncogenic functions. The LT antigen that is expressed in nuclei of the tumor cells is able to bind and sequester Rb through a conserved LxCxE motif [14]. Furthermore, the integration of MCPyV into the host cellular genome is also considered as a key element in oncogenesis [14].

Recently, Hashida *et al.* [16] reported for the first time the prevalence of MCPyV in lung cancers in an Asian population and detected MCPyV DNA in 17.9% (20/112) of Japanese NSCLCs. The differences in the detection rates from Caucasian patients may be explained in part by geographic epidemiological variations in patients with NSCLC or merely by the technical approaches used. Importantly, the Japanese research group found two NSCLC cases infected with MCPyV carrying a tumor-specific signature. The cases had the LT oncoprotein expressed in the cancer cells, the tumor-specific truncated *LT* gene with a preserved Rb-binding domain, and the integrated viral genome into chromosomes of cancer cells [16]. Thus, the integrated/mutated forms of MCPyV are demonstrated for the first time in a specific cancer other than MCC, suggesting that MCPyV is associated with the pathogenesis of NSCLC in a subset of patients.

The underlying tumorigenic mechanisms of MCPyV in NSCLC have not yet been fully elucidated. A hypothesis can be raised: long-standing exposure of the lower respiratory tract to MCPyV might cause viral integration, and subsequent expression of the LT antigen may lead to the oncogenic transformation of the MCPyV-infected cells. The viral integration might also promote cellular gene alterations during the multistep tumorigenesis process. Houben *et al.* [17] proposed new evidence that MCPyV is necessary for initiation of the tumor, but that the additional cellular gene mutations may render MCPyV irresponsible for tumorigenesis. In this context, it is important to determine the expression profiling of cellular genes involved in carcinogenesis in MCPyV-associated NSCLC. A Greek research group reported a downregulation of the *Bcl-2* gene and an upregulation of the *BRAF* gene in MCPyV DNA-positive NSCLCs [13]. On the other hand, a Japanese research group showed a trend toward higher expression levels of the *Bcl-2* gene in MCPyV-positive NSCLCs and a statistical significant correlation of the *Bcl-2* upregulation was found in MCPyV-positive adenocarcinomas [18]. Asians and Caucasians have different genetic susceptibilities to lung cancer, as evidenced by gene polymorphisms and genome-wide association studies. For example, east Asian patients with NSCLC have a much higher prevalence of mutation of the *EGFR* gene and a lower prevalence of mutation of the *K-ras* gene. The clinical and genetic differences between lung cancers in east Asians and Caucasians may be related to the discrepancy of the gene expression profiling in MCPyV-positive NSCLCs. In fact, Xu *et al.* [19] reported that the presence of MCPyV LT DNA is correlated with the *EGFR* mutations in Chinese patients with NSCLC.

Another important question to be addressed is whether incidence of MCPyV-associated NSCLC is influenced by exposure to risk factors such as smoking. The Japanese research group showed a trend toward a higher detection rate of MCPyV in never smokers than in smokers [16]. Similarly, other studies reported higher incidences of HPV DNA in lung cancers from Asian cohorts, especially among never smokers [1]. On the other hand, the Greek research group reported a positive trend for smoking status in MCPyV-positive NSCLCs [13]. It is shown that the incidence of lung cancer in never smokers varies between geographic locations or ethnic groups [1,2]. The higher prevalence of NSCLC occurring in never

“Another important question to be addressed is whether incidence of Merkel cell polyomavirus-associated non-small-cell lung cancer is influenced by exposure to risk factors...”

smokers in Asia may account for the discordance between the two research groups.

Hashida *et al.* [20] reported interesting findings from phylogenetic analyses based on the nucleotide sequences of the full-length MCPyV *LT* gene derived from cancer samples including MCC and lung cancer in Japanese patients and those from MCC samples in Caucasian patients. The phylogenetic analyses identified two main genetic clades. One clade comprised strains isolated from Caucasians, whereas all of the Japanese tumor-derived MCPyV strains belonged to another clade. These findings indicate that different MCPyV genotypes are prevalent in geographically distinct human populations. Further studies will elucidate whether distinct MCPyV genotypes are correlated to the clinical and genetic differences between MCPyV-positive NSCLCs in east Asian and Caucasian patients.

In summary, detection of MCPyV with a tumor-specific signature in lung cancer suggests a direct or indirect pathogenetic role of MCPyV in NSCLC. Determining the factors that contribute to the persistence infection of MCPyV in the lower airways is also an important issue. Worldwide study of the pathogenetic relevance of MCPyV in lung cancer is becoming a promising project.

Financial & Competing Interests Disclosure

This work was supported by JSPS KAKENHI (M Daibata). The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

“Worldwide study of the pathogenetic relevance of Merkel cell polyomavirus in lung cancer is becoming a promising project.”

References

- Couraud S, Zalcman G, Milleron B, Morin F, Souquet PJ. Lung cancer in never smokers – a review. *Eur. J. Cancer* 48, 1299–1311 (2012).
- Dela Cruz CS, Tanoue LT, Matthy RA. Lung cancer: epidemiology, etiology, and prevention. *Clin. Chest. Med.* 32, 605–644 (2011).
- Prabhu PR, Jayalekshmi D, Pillai MR. Lung cancer and human papilloma viruses (HPVs): examining the molecular evidence. *J. Oncol.* 2012, 750270 (2012).
- Goto A, Li CP, Ota S *et al.* Human papillomavirus infection in lung and esophageal cancers: analysis of 485 Asian cases. *J. Med. Virol.* 83, 1383–1390 (2011).
- Gómez-Román JJ, Martínez MN, Fernández SL, Val-Bernal JF. Epstein–Barr virus-associated adenocarcinomas and squamous-cell lung carcinomas. *Mod. Pathol.* 22, 530–537 (2009).
- Trejo-Avila LM, Zapata-Benavides P, Barrera-Rodríguez R *et al.* Mouse mammary tumor-like gene sequences are present in lung patient specimens. *Virol. J.* 8, 451 (2011).
- Feng H, Shuda M, Chang Y, Moore PS. Clonal integration of a polyomavirus in human Merkel cell carcinoma. *Science* 319, 1096–1100 (2008).
- Babakir-Mina M, Ciccozzi M, Lo Presti A, Greco F, Perno CF, Ciotti M. Identification of Merkel cell polyomavirus in the lower respiratory tract of Italian patients. *J. Med. Virol.* 82, 505–509 (2010).
- Andres C, Ihrler S, Puchta U, Flaig MJ. Merkel cell polyomavirus is prevalent in a subset of small cell lung cancers: a study of 31 patients. *Thorax* 64, 1007–1008 (2009).
- Helmbold P, Lahtz C, Herpel E, Schnabel PA, Dammann RH. Frequent hypermethylation of *RASSF1A* tumour suppressor gene promoter and presence of Merkel cell polyomavirus in small cell lung cancer. *Eur. J. Cancer* 45, 2207–2211 (2009).
- Joh J, Jensen AB, Moore GD *et al.* Human papillomavirus (HPV) and Merkel cell polyomavirus (MCPyV) in non-small cell lung cancer. *Exp. Mol. Pathol.* 89, 222–226 (2010).
- Gheit T, Muñoz JP, Levican J *et al.* Merkel cell polyomavirus in non-small cell lung carcinomas from Chile. *Exp. Mol. Pathol.* 93, 162–166 (2012).
- Lasithiotaki I, Antoniou KM, Deras SP *et al.* The presence of Merkel cell polyomavirus is associated with deregulated expression of *BRAF* and *Bcl-2* genes in non-small cell lung cancer. *Int. J. Cancer* 133, 604–611 (2013).
- Shuda M, Feng H, Kwun HJ *et al.* T antigen mutations are a human tumor-specific signature for Merkel cell polyomavirus. *Proc. Natl Acad. Sci. USA* 105, 16272–16277 (2008).
- Houben R, Shuda M, Weinkam R *et al.* Merkel cell polyomavirus-infected Merkel cell carcinoma cells require expression of viral T antigens. *J. Virol.* 84, 7064–7072 (2010).
- Hashida Y, Imajoh M, Nemoto Y *et al.* Detection of Merkel cell polyomavirus with a tumour-specific signature in non-small cell lung cancer. *Br. J. Cancer* 108, 629–637 (2013).
- Houben R, Grimm J, Willmes C, Weinkam R, Becker JC, Schrama D. Merkel cell carcinoma and Merkel cell polyomavirus: evidence for hit-and-run oncogenesis. *J. Invest. Dermatol.* 132, 254–256 (2012).
- Hashida Y, Imajoh M, Daibata M. Gene expression analysis in Merkel cell polyomavirus-positive non-small cell lung cancer from Japanese patients. *Int. J. Cancer* 133, 3014–3015 (2013).
- Xu S, Jiang J, Yu X, Sheng D, Zhu T, Jin M. Association of Merkel cell polyomavirus infection with *EGFR* mutation status in Chinese non-small cell lung cancer patients. *Lung Cancer* 83, 341–346 (2014).
- Hashida Y, Imajoh M, Kamioka M *et al.* Phylogenetic analysis of Merkel cell polyomavirus based on full-length *LT* and *VPI* gene sequences derived from neoplastic tumors in Japanese patients. *J. Gen. Virol.* 95, 135–141 (2014).