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Molecular pathological findings of Merkel cell polyomavirus in lung cancer: A possible etiopathogenetic link?

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Dear Editor,

The proportion of cancers caused by infectious agents, including bacteria, parasitic worms and viruses, was recently estimated to be more than 20%,[1,2] while the contribution of several viruses is particularly high in certain types of cancer.[3]

Over 50 years of polyomavirus research has provided novel insights into not only the general biological functions in mammalian cells but has also provided a great deal of information as to how conditions can be altered and signaling systems tweaked to produce transformation phenotypes.[4–6] Over the past few years, three new members (KIV, WUV and MCPyV) have joined the two previously known (JCV and BKV) human polyomaviruses.[4–6] MCPyV was the third novel polyomavirus identified in a rare but aggressive skin cancer of neuroendocrine origin, termed Merkel cell carcinoma.[7]

We appreciate the comments of the Japanese research group (submitted letter IJC-13-0568), giving us the opportunity to further discuss the role of polyoma viruses, and particularly that of Merkel virus, in lung carcinogenesis, as a number of studies have recently been published in this interesting research field.[8–11]

Polyoma viruses, such as BK virus (BKV), JC virus (JCV) and MCPyV are typically non-oncogenic. The evidence for their role in human cancer remains controversial, although they have been detected in a variety of human neoplasms.[2] The aforementioned viruses BKV, JCV and SV40, or their early proteins can induce tumors in animal models, and can immortalize or transform cultured cells, including human cells.[4,12] However, similar studies on the newly discovered polyoma viruses are lacking.

We have read with great interest the commentary by Hashida *et al* (submitted letter IJC-13-0568), as the authors have shown for the first time in their original study, a prevalence of 17.9% for MCPyV in non-small cell lung cancer (NSCLC) in an Asian population. The current literature in lung cancinogenesis and more specifically in NSCLC has detected a varying prevalence for MCPyV from 5% in Chile,[11] 9.1% in Greece[8] to 16.7% in North America.[10] It should also be noted that both HPV and MCPyV are directly associated with 33% of NSCLC cases. Moreover, our preliminary data indicate that in the same set of samples,[8] HPV DNA is detectable in 19% of the specimens (unpublished data).

We are of the opinion that these variations in prevalence between studies from different geographical regions emphasize the complexity of regulation levels at different stages in carcinogenesis. Recently, the interplay of the microenvironment, pathogens, immunity, inflammation, cellular epigenetic alterations and various chronic diseases has attracted increasing attention.[12–14] Previous studies thus far have shown that factors, such as disease stage, clinical parameters and methodological issues are rather minor issues. It is becoming more evident that further studies are required to determine whether polyomavirus may be placed among the determinants of risk.

Smoking is a major risk factor for lung cancer and it is recognized as having a critical epigenetic effect. In the Japanese study, 68.8% (22 out of 32) of women and 6.3% (5 out of 80) of men with lung cancer were never-smokers.[9] However, among the number of samples positive for the presence of MCPyV, only one had a negative smoking history, while the mean pack-year history was increased in our study.[8] On the other hand, Hashida and coworkers showed a trend toward a higher detection rate of MCPyV in never-smokers (submitted letter IJC-13-0568). A similar trend has been also observed in studies on HPV in Asian cohorts (16). We fully agree with our Japanese colleagues that this discrepancy is due to the different epidemiology of lung cancer in Asia.[9]

As regards the possible oncogenic effect of Merkel cell polyomavirus, it is known that MCPyV large T antigen contains merkel cell carcinoma (MCC) tumor-specific mutations that ablate its replication capacity but preserve its oncogenic functions, and the small T antigen promotes an environment favorable for cap-dependent translation.[4,9] In our study, we describe for the first time, a possible oncogenic mechanism for MCPyV, as we observed a downregulation of the *Bcl*-2 gene and an upregulation of the *BRAF* gene in MCPyV-positive patients.[8] On the other hand, the results of the Japanese study show a non-statistical trend toward higher expression levels of the *Bcl*-2 gene in MCPyV-positive samples (submitted letter) and a statistical significant correlation occurring only in adenocarcinoma-positive samples. In our study,[8] *Bcl*-2 expression was found to be downregulated in the NSCLC samples compared to the controls ($p = 0.047$),

while Bcl-2 gene expression was found to be downregulated in the MCPyV-positive specimens ($p = 0.050$) with a literally border line statistical significance.[8] Additionally, we have no data regarding the Bcl-2 expression levels among the positive and negative adenocarcinomas.[8]

The importance of tumor–host interactions, encompassing pathogens and inflammation, has been highlighted by the recent discovery of a continuum in the frequency of molecular features (including BRAF mutation) in colorectal cancers.[15]

As the Japanese authors discuss in their letter, Asian patients with NSCLC have a much higher prevalence of mutation of the epidermal growth factor receptor gene and a lower prevalence of mutation of the K-ras gene (submitted letter IJC-13-0568). RAS and several of its downstream effectors, including BRAF, have been shown to be commonly mutated in broad range of human cancers.[16–19] With the identification of RAS mutation as a strong predictor of clinical resistance to epidermal growth factor receptor (EGFR)-targeted therapies, RAS mutational testing has been incorporated into the routine clinical care of patients with colorectal and lung cancers.[15] It becomes obvious that determining the molecular and viral profiling in lung cancer patients would be a cardinal next step in order to control this lethal disease. Furthermore, the investigation of the interactions between the host and MCPyV should not be limited to the genetic level but should be expanded to the epigenetic mode of gene regulation induced after viral infection.[2,14] The role of microRNAs, either virally expressed or virally induced in the host would also be of great interest in MCPyV-infected NSCLC, revealing novel modes of crosstalk between the virus and the host.[20] Several studies on breast and bladder cancer cells have demonstrated that inhibiting histone deacetylase (HDAC) activity has significant impact on miRNA expression.[21] However, the effect of HDAC inhibitors seems to be tissue-specific, as similar treatment on NSCLC cell has little effect on miRNA expression.[21]

The detected prevalence of MCPyV in NSCLC may suggest a pathogenetic role of this virus in NSCLC of the lung. These results implicate MCPyV mainly in lung adenocarcinoma, while they also provide evidence of the potential oncogenic role of this virus in NSCLC. As it is evident from the aforementioned literature, the mechanisms of MCPyV-induced transformation have not yet been fully elucidated, but the likely etiological role of this new polyomavirus in human cancer provides a strong opportunity to expand the knowledge of virus–host interactions and viral oncology.

Yours sincerely,
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