Epstein-Barr virus (EBV) ubiquitously infects human beings and is associated with several malignancies. However, the mechanism of the viral oncogenicity remains largely to be understood. In our investigations, we have reported a tumor model in which that EBV facilitated the tumorigenesis in epithelial cells latently infected by EBV genome. Using this model, we have found several clues and further confirmed them for the viral pathogenesis. We have recently reported that the EBV copy number is related with the potential malignancy of the infected cells, corresponding to the activation level of LMP1 and NF-κB signaling. Though the DNA load in patient blood has been well-documented as a potential indicator of EBV-related diseases, this was the first experimental model to verify that the EBV copy number in cancer cells directly correlates with the tumorigenesis. We emphasize that not only “with or without” but also “more or less” should be concerned in EBV-related approaches at the gene expression level or in genome context.

Keywords: Epstein–Barr virus; latent membrane protein 1; copy number; oncogenicity

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Epstein-Barr virus (EBV) is a member of herpesvirus family that establishes a life-long persistence in human host[1, 2]. The virus has a large complex genome with 172kb of dsDNA. It infects adult population broadly and is known for its close association with several malignancies, including Burkitt’s lymphoma and nasopharyngeal carcinoma (NPC). The findings of EBV in NPC and gastric carcinoma have revealed that EBV can infect epithelial cells which do not have the receptor CR2 as in B lymphocytes for the viral infection[4]. The lack of cell models of EBV-infected epithelial cells is still a problem in the related study. Therefore, it becomes more mystified for the pathogenesis of this ubiquitous virus. It is also hard to explain the link between the high infection rate and low tumorigenicity rate, which is not consistent with the characteristics of tumor viruses such as hepatitis B virus or human papillomavirus[5]. The answer is usually obscure as that multiple factors are involved in the development of cancer.

We have recently reported an unexpected finding that the EBV-encoded oncoprotein LMP1 is involved in the viral genome restriction in a human embryonic kidney epithelial cell model[6]. The replacement of intact NPC-LMP1 in the B95-8 genome resulted in low copy number of EBV in the latent infected cells and low malignancy. In the cells harboring high copy number of EBV, the transcription and
expression of LMP1 was also high. The consequence of this effect was that the activation of nuclear factor NF-κB was at high level (Figure 1). As mentioned above, there is no effective epithelial cell model to be used broadly for the study of EBV oncogenicity. We previously used HEK293 cells with low malignant potential to establish a model that EBV facilitates the tumorigenicity of infected cells [7]. We have used this model to find some clues for the mechanism study of EBV oncogenicity. The LMP1-modulated microRNA-203 was an example. The miR203 was found to be down-regulated in 293-EBV cells, and was validated to be consistent in NPC tissues [8]. The miR-203 expression is also dependent on NF-κB [8] (Figure 1). Though EBV latently infected HEK293 is not particularly relevant for EBV infection, our results have shown that it is useful to find EBV-related potential mechanism. Using this model, we presented the first evidence by experimental model that the copy number of EBV correlates with the viral pathogenesis [6]. In this approach, the average copy number of EBV genome was found more receivable than the total copy number to assess the tumorigenicity of a group of EBV-positive cancer cells.

It has been noticed that EBV DNA load in tumor tissues or blood is associated with the clinical progression and prognosis in both lymphoma and NPC [9-11]. With the improved technique of real-time quantitative PCR, more recent studies have shown that detection of viral DNA in the sera of patients is informative [12-14]. Quantitative serological analysis of EBV copy number should be an important indicator for EBV infection especially in an immunocompromised patient whose EBV specific antibody such as anti-VCA IgA may be at very low levels [15]. Combined with our experimental results, we propose that EBV load should be considered into the etiological study of related cancers. In other words, in any case in the viral gene expression or genome context, being “more or less” should be concerned instead of mere “with or without” for the virus. Based on our results, there is a reason to speculate that one cell with very low EBV copy number might not be transformed easily, let alone to develop a cancer. This may partly explain the fact that this ubiquitous virus is associated with only a minority of related cancers.

In our later study, we have verified the expression level of miR-203 which was found downregulated by LMP1 previously corresponds to the level of EBV copy number in the EBV-infected cells with different EBV copies. The related study is underway and would be reported elsewhere. Besides, we will try to find precise functional domains or sites in LMP1 responsible for the genome restriction.

In summary, we have found that the EBV oncoprotein LMP1 is involved in the viral genome compatibility, raising a new concern that LMP1 becomes one determinant of EBV copy number in the latent infection. The copy number level is directly associated with the activation level of LMP1 and NF-κB. We emphasize again that the level of gene expression or genome load should be concerned in the related study. EBV load is able to be continuously used as a marker of related diseases in the prognosis and progression.

Conflicting interests

The authors have declared that no conflict of interests exist.

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Abbreviations

EBV: Epstein–Barr virus; LMP1: latent membrane protein 1; NPC: nasopharyngeal carcinoma; VCA: viral capsid antigen; NF-κB: nuclear factor κB.

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