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Epstein-Barr Virus (EBV) Genome Sequence Variations, Virus Strain Classifications and EBV-Associated Tumors

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Mini Review

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Abstract

The Epstein-Barr virus (EBV), a member of the *Herpesviridae* family, belonging to the *Gammaherpesvirinae* subfamily, has been associated with several nonmalignant and malignant diseases, including Burkitt's lymphoma, gastric cancer, Hodgkin's lymphoma, and nasopharyngeal carcinoma.

In recent years numerous EBV genome sequences have been analyzed to answer the question of whether EBV genome variations are tumor-specific, ethnically or geographically determined. A clear answer regarding the "specialization" of EBV strains has not yet been received; however, attempts are being made to identify high-risk EBV strains. This mini-review analyzes the most well-known EBV classifications, EBV sequence variations and their association with EBV-associated human pathologies.

Keywords: Epstein-Barr Virus Classification; Population; Environmental Factors

Mini Review

The wide spread of EBV among the world's population, as a rule, does not lead to the development of malignant tumors in infected individuals. For tumor occurrence, a number of additional factors are required, due to which the transforming potential of the virus can be included in the pathological process leading to the emergence of malignancies. For different pathologies, these factors can vary significantly. The most common of them include unfavorable environmental factors (carcinogenic, chemical, radiation and other pollution), immune suppression, as well as a genetic predisposition to a particular neoplasm.

The structure of EBV genome and the biological characteristics of the virus play an equally important role in EBV-associated carcinogenesis. Studies have shown that there are two main genotypes of the virus, EBV-1 and EBV-2 (Type A and type B) differing in the sequences of nuclear antigens (EBNA2 и EBNA -3A, -3B и -3C) and occurring with unequal frequency in different geographic regions of the planet. Their phenotypic difference lies in the more powerful *in vitro* transforming activity of the 1st type of the virus compared to the 2nd one [1]. In contrast to the prototype B95.8 virus strain ("F" variant), another strain (variant "f"), which has an additional BamHl site in the BamHl F region, was found almost exclusively in patients with nasopharyngeal carcinoma (NPC) in the southern provinces of China [2].

Based on the sequence analysis of the C-terminal region of the LMP1 protein, EBV strains have been subdivided into separate variants on the basis of the most characteristic LMP1 mutations. One of the classifications widely used so far includes protein variants, the designation of which is

[China 1 (Ch1), China 2 (Ch2), China 3 (Ch3), Mediterranean + (Med +), Mediterranean - (Med-) and Northern Carolina (NC)] reflected their geographical origin [3]. Each of above LMP1 variants was characterized in detail for its ability to transform mammalian cells (Rat-1), induce the activation of the transcription factor NF-kB, and bind one of the cellular proteins from the E3 family of ubiquitin ligases (HOS/ β-TrCP) [4]. It is important to note that nucleotide substitutions in genes encoding various LMP1 variants are usually located in regions that control the transcription or translation stages. Amino acids of the corresponding coding proteins affect functional activity and immunogenicity, half-life, or transforming potential of LMP1 [5]. LMP1 activation of a number of transcription factors (NF-kB, AP-1, STAT) changes the profile of intracellular activity of a number of signaling pathways [6]. In particular, LMP1 suppresses (usually indirectly) the expression of a number of key tumor suppressors (p53, RASSF1A, survivin), disrupts the work of the G1-S cell cycle checkpoints, ensuring the survival of damaged cells [7,8]. LMP1 also induces the expression of pro-inflammatory cytokines, endows infected cells with resistance to apoptosis, induces epithelial-mesenchyme transition (EMT), enhances cell motility, their invasion and metastasis, selectively suppresses or activates the expression of a number of cellular micro-RNAs etc [9,10].

Direct sequencing of the C-terminal domain of LMP1 (showing a high degree of heterogeneity compared to other EBV genes) in biological materials (blood, saliva, and tumor tissue) of cancer patients and healthy individuals from different geographic regions revealed mismatched LMP1 variants. Thus, new variants of the LMP1 protein, which are recombinants of the Raji and China variants, were found in Argentina [11]. Three specific LMP1 variants (CG1-1, 2, 3) have been identified in Chinese Hodgkin' lymphoma (HL) patients [12]. Two new LMP1 variants, Southeast Asia 1 (SEA 1) and Southeast Asia 2 (SEA 2) have been identified in southern Thailand [13]. A variant of TatK-LMP1, characterized by two atypical 5 aa deletions in codons 312-316 and 382-386, respectively, was found in ethnic Tatars in Russia [14].

The growing number of published EBV genome sequence variations raises the question of whether these variations are tumor specific, as well as ethnically and geographically determined. In contrast to the recognition of high-risk papilloma viruses, a clear answer regarding the "specialization" of EBV strains has not yet been received; however, attempts to detect high-risk EBV variants are being made.

Recently, it was demonstrated that among various EBV strains persisting in the population, there are variants that replicate more efficiently in primary B-cells than others and, therefore, are potentially more pathogenic. These strains represent a risk factor for the development of some EBV-associated lymphomas and carcinomas [15]. The Chinese NPC-derived EBV M81 strain showing B-cell proliferative activity and high propensities to infect epithelial cells represents one of such strains [16].

It has been proven, that in EBV genome the recombination events occur 2.5-times more often than mutations, suggesting that recombination has a much stronger impact in EBV genomic diversity than mutations. Using the Hierarchical Bayesian analysis of EBV population structure (hierBAPS), Zanella, et al. [17] selected 12 EBV populations associated with geographic location, of which three Asiatic populations (EBV-p1/Asia/GC, EBV-p2/Asia II/Tumors and EBV-p4/China/NPCs) were linked to tumor development. Authors further demonstrated marked geographic circulations of diverse EBV populations, one of which have been detected for populations of four Asian countries (China, Japan, Korea and Vietnam), two EBV populations have been exclusively circulating in Kenya, and other six EBV populations have shown a broader geographical circulation. It is important to note that with some exception among the Asiatic EBV populations, an EBV-p1/Asia I population, dominantly associated with gastric cancer, the EBVp4/China population was more frequently associated with nasopharyngeal carcinoma (NPC), and the EBV-p2/Asia II population showed predominant association with several types of tumors and lymphoproliferative disorders [17].

Lam, et al. [18] using full-length sequencing of the EBV genome from plasma samples of NPC patients and healthy virus carriers, found that these viral genomes differ in the frequency of single nucleotide variants (SNV). They also suggested the presence of NPC-associated EBV SNV profile and proposed the NPC risk score on an individual basis in persons carrying NPC-associated variants of the virus.

Thus, the advances in the identification of tumor-derived and ethno-geographically-derived EBV strains obtained by sequence analysis of viral isolates of various origins, made an important contribution to understanding the biological nature of this virus and provide a basis for future, more directed analysis of association of specific EBV variations with EBV biology and EBV-associated diseases. Further study of EBV strain variation and functional properties of NPC-associated EBV strains seems to be also important for clinical application. The identification of groups of people infected with NPC-associated EBV strains should have significant impact on the early diagnosis of NPC. A significant contribution may be also done for development of an effective EBV vaccine.

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