Epstein-Barr Virus – pathogenesis, latency and cancers

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Abstract

The Epstein-Barr virus (EBV) was discovered in 1964 by Michael Anthony Epstein and Yvonne Barr, who discovered a herpesvirus-like infectious agent in a biopsy specimen from a patient with Burkitt's lymphoma. This virus belongs to the Herpesviridae family (subfamily Gammaherpesvirinae, genus Lymphocryptovirus). EBV is a ubiquitous herpesvirus that is causally associated with various malignant tumours. According to the current nomenclature, it was named human herpesvirus type 4 (human herpesvirus 4 – HHV-4). Primary infection usually occurs in childhood. In developing countries, the infection rate among young children is higher than in developed countries. It was the first human tumour virus and it is currently categorized as a group-1 carcinogen due to its association with various cancers. It is estimated that over 90% of the adult population has been infected with this pathogen, but only a minority will develop the disease. EBV establishes latent infection characterized by the expression of a limited number of viral genes called latent genes. Moreover, during its life cycle, EBV periodically reactivates and can be transmitted to other susceptible hosts. The oral cavity is the main site of EBV occurrence and the most common source of infection. This study discusses EBV frequency and its association with the occurrence of malignant tumours and the pathways of tumour progression.

Key words

EBV, latency, infection, cancer

INTRODUCTION

The Epstein-Barr virus (EBV) is a ubiquitous herpesvirus that is causally associated with various malignant tumours. Antibodies to the Epstein-Barr virus are detected in approximately 95% of the human population. Primary infection usually occurs in childhood. In developing countries, the infection rate among young children is higher than in developed countries [1, 2]. The Epstein-Barr virus spreads through the air-droplet tract, saliva, transfusion of blood and blood products, transplantation and sexual intercourse [1]. The virus, when it becomes latent, can survive in the body for the rest of its life [3]. The main objective of this literature survey is to show the problem of the large number of people infected with EBV virus, and many diseases related with this virus, for example, with cancer.

The viral infection in the world. The disease associated with EBV infection was first described by Filatov and Pfeiffer (symptoms: malaise, fever, hepatosplenomegaly and lymphadenopathy). It was called glandular fever [4]. In 1921, Sprunt and Evans observed leukocytosis with mononuclear cells in young people who had similar clinical symptoms. In 1925, Davidsohn found that antibodies present in the serum of infectious mononucleosis patients agglutinate sheep and horse erythrocytes. The observations by Paul, Davidsohn and Bunnell led to the development of a slide test, called the PBD test (Paul-Bunnell-Davidsohn test), which was later applied in a laboratory diagnosis of infectious mononucleosis [2].

The virus was discovered in 1964 by Michael Anthony Epstein and Yvonne Barr, who discovered a herpesvirus-like infectious agent in a biopsy specimen from a patient with Burkitt's lymphoma [5, 6]. The Epstein-Barr virus belongs to the Herpesviridae family (subfamily Gammaherpesvirinae, genus Lymphocryptovirus). According to the current nomenclature, it was named human herpesvirus type 4 (human herpesvirus 4 – HHV-4). Its only natural host is the human being [1]. The incubation period usually lasts from 30 – 50 days. Primary infection is usually asymptomatic or shows only minor symptoms. The most common form of symptomatic infection is infectious mononucleosis – a sharp, self-limiting lymphoproliferative reaction [7]. Symptoms of infectious mononucleosis include fever, pharyngitis and tonsillitis, enlargement of the lymph nodes, liver and spleen. These symptoms may be accompanied by rash, upper eyelid oedema, nasal congestion, eczema on the palate, and muscles and joint pain. In the peripheral blood morphology, leucocytosis with lymphocytosis and atypical lymphocytes, which represent more than 10% of the total number of white blood cells, are found. [8].

There are two subtypes of this virus, EBV1 and EBV2, which differ in geographic distribution, but the clinical course of the disease is similar. Subtype 1 predominates in Europe, whereas subtype 2 in Africa. Homology between the nucleic acids of both subtypes is 70 – 85%, and the difference lies in the nucleic acid coding region (EBNA) and two short, non-coding RNA chains (EBER) [3]. Infection with one subtype of the virus does not exclude superinfection with the other, therefore co-infection is possible.

The virus particle is approximately 122 – 180 nm in diameter and is composed of double strand DNA which contains about 172 kb and 85 genes. The DNA is surrounded by a protein nucleocapsid. This nucleocapsid is surrounded by

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a tegument made of protein, which in turn is surrounded by a lipid envelope. The surface glycoproteins play an important role in the virus adsorption phase and then in the virus entry into the cell. The Epstein-Barr virus genes encode 100 – 200 polypeptides [9]. Primary infection occurs in the nasopharyngeal cavity, where virions fuse with epithelial cells and B lymphocytes cells. In the adsorption phase, the virus binds via gp350 and gp220 envelope glycoproteins with the CD21 cellular receptor, which is also a receptor for C3d complement and which then infiltrates into B cells. Nucleocapsid is released into the cytoplasm, and viral DNA enters the nucleus of the cell, where it replicates. It takes the form of an extrachromosomal, circular episome, characteristic of the latent phase. In the lytic phase, it can integrate with chromosomes and occur in the form of linear DNA [10].

Latency. The Epstein-Barr virus, like other herpesviruses, is able to cause a latent infection. In the latency phase, the expression of proteins occur, i.e. nucleic proteins: EBNA-1, -2, -3A, -3B, -3C, -LP, three membrane proteins: LMP-1, -2A, -2B and RNA transcripts: EBER- 1, -2, which protect the virus from being eliminated by the host's immune system. In the latent phase, the virus genome is replicated only once in the cell cycle. Depending on the expression of antigens, there are three types of latency:

Type I – expression of the EBNA-1 nuclear antigen and two small nuclear non-coding RNAs: EBER-1, EBER-2;

Type II – additional expression of membrane proteins: LMP-1, LMP-2A, LMP-2B;

Type III latency, the most immunogenic, synthesis of nuclear antigens: EBNA-1, EBNA-2, EBNA-3A, EBNA-3B, EBNA -3C, EBNA-LP, all LMP and EBER proteins [8,11,12].

Moreover, in all types of latency there are also transcripts from the BamH1A genome of the virus, the function of which has yet to be explained [8].

Table 1. Expression of EBV viral genes in different types of latency [13].

EBV	Gene Expression	Disease Entity
Type 0	EBERs	B cell proliferation
Type I	EBERs, EBNA1, BARTs	Burkitt's lymphoma, Hodgkin's disease
Type II	EBERs, EBNA1, LMPs, BARTs	Nasopharynx cancer, stomach cancer
Type III	EBERs, EBNA1, EBNA-LP, EBNA2, EBNA3A, EBNA3B, EBNA3C, LMPs	Lymphopriliferative diseases PTLD

Latent phase proteins. EBNA-1 is a DNA-binding phosphoprotein and, together with a fragment of the OriP genome, it is responsible for the replication of the virus. The OriP region of the virus genome contains two 18pz binding sites of EBNA-1. Other EBNA-1 binding sites are in +10 and +34 nucleotides down from the Qp promoter. The Qp promoter secures and maintains an adequate level of EBNA-1 protein. The binding of EBNA-1 to the Qp promoter leads to a decrease in its expression by negative feedback [12]. EBNA-1 also preserves the virus's DNA in episomal form during latency. It occurs in all types of latency and also during the activation to the lytic cycle. It is a transcriptional activator and increases the expression of LMP1 [4]. EBNA-1 is involved in the regulation of the transcription factor, which has properties of the tumour suppressor p53 [12]. It is a non-immunogenic protein, undetectable by cytotoxic T lymphocytes. This is due to the occurrence of amino acid triplet gly-gly-ala, which prevents virus degradation and virus antigen presentation by cytotoxic T lymphocytes by HLA I, resulting in impaired cellular responses [14, 15, 16]. It will thus condition the survival of infected B lymphocytes.

EBNA-2 is a major contributor to the immortalization of B lymphocytes. EBNA-2 activates c-myc protooncogens and c-fgr and maintains cell proliferation after infection. It is a transcription factor that regulates the expression of both viral and cellular genes. It increases the expression of LMP1, LMP2A and LMP2B. The existence of two types of EBNA-2 forms the basis for the isolation of the two subtypes of the virus, i.e. EBV1 and EBV2. [15, 16, 17].

EBNA-3A, -3B, -3C are proteins encoded by three adjacent genes located in the middle of the virus genome. They induce an enhanced host immune response and are essential in the process of B cell immortalization.

EBNA-LP regulates the process of apoptosis of cells infected by EBV.EBNA-LP. EBNA-2 appears in the early phase of infection and leads to the transition of resting B cells to G1 phase of the cell cycle. EBNA-LP forms the HAX-1 complex (HS-1-associated protein X-1) formed by binding to the ISI and X-1 cellular proteins. The amino acid sequence in the resulting complex is similar to the Nip3 cellular protein (nineteen kD inter-acting protein-3), which interacts with the Bcl-2 apoptosis inhibitor or its viral BHRF-1 counterpart, regulating apoptosis of infected B lymphocytes [12].

In the latent phase, two short RNA chains are present in the nucleus – EBER1 and EBER2 – containing 166 and 172 bases, respectively [3]. They are products of the transcription catalyzed by polymerase III and they regulate translation and transfer of information.

LMP-1 is a 63 kDa membrane protein consisting of three domains. LMP-1 has an affinity for proteins which have receptors for the tumour necrosis factor. LMP-1 causes intracellular activation of anti-apoptotic transcription factors: nuclear kappa B (NF-κB), activator protein AP-1 and STAT-1. The increased activity of transcription factor NF- κB interferes with the cell metabolism (as a result of over-expression of the genes involved in apoptosis regulation) and the course of the cell cycle [11, 14, 18]. By B-lymphocyte activation, LMP-1 increases the production of interleukin 6, 8, 10. LMP-1 also increases the expression of Bcl-2, Mcl-1 and A2O genes, which protect infected B cells against p53-dependent apoptosis [15, 16].

The EB virus strains with the unchanged LMP-1 gene are referred to as the wild-type virus (wt-LMP-1), while strains with 30 base pairs deletion in LMP-1 are referred to as deltas (del-LMP-1). The EBV del-LMP-1 type exhibits a greater oncogenic potential and, on the other hand, is less immunogenic in comparison with the wild-type virus [19].

The LMP-2 gene encodes two proteins: LMP-2A and LMP-2B, which are expressed in the latent phase. It is believed that both proteins affect oncogenesis. However, their role has not yet been thoroughly explained [13].

EBV infection. The reduced immunity of the host's body, caused by various factors (immunosuppressive treatment, steroid hormone therapy), may induce viral reactivation and transition of the latent phase into the lytic phase [20, 21].

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During primary acute infection, the lytic cycle lasts longer than in the case of virus reactivation. The genetic material of the virus occurs in the form of linear DNA, which in the nucleus of the host undergoes replication and transcription, using the host enzyme system. In the process of translation, viral proteins are produced in the cell's cytoplasm.. In the early lytic phase, the genes of proteins involved in viral DNA replication are primarily expressed. The first protein in the course of the lytic cycle of the virus is Z protein, also called Zta or ZEBRA. It is a product of the BZLF1 gene and it stimulates the activity of the BRLF1 gene to produce protein R. Proteins Z and R activate each other and, when they reach a high level, they stimulate the synthesis of the proteins needed to replicate the virus. Other proteins which appear in the early phase of the lytic cycle are the products of the BSMLF1 and BMRF1 genes. In the late phase, proteins involved in the construction of the capsid and the formation of new viral particles are synthesized. Genes of the viral capsid antigen complex (VCA) and of EA (Early Antigen Diffuse and Early Antigen Restricted EA) antigens are subject to expression. The EA-D form is detected in the cell nucleus and cytoplasm, and EA-R form in the cell nucleus only. Serological diagnosis of EBV infections makes use of the presence in the serum of specific antigen antibodies (EBVCA) in the IgM and IgG class, nuclear antigen (EBNA) and early antigen (EA) antibodies [22]. In primary infection, EBV is not detected in the blood; however, it can be detected in a large titer in the oral cavity, where the virus can be present for many years in healthy individuals. In the initial phase of most infected patients, EBVCA can be detected in the IgM class which tends to fall within 2 – 6 weeks. Approximately two weeks after infection, EBVCA can be detected in the IgG class and it lasts throughout life. EBNA1 IgG appear approximately 3 – 6 months after infection, and are also present in serum throughout life [22].

EBV-related cancers. Chronic infections and reactivation of latent infection are especially dangerous in the case of patients with congenital or acquired immunodeficiency, as well as those treated immunosuppressively, where the mortality rate can be up to 40%.

Cancers associated with EBV infection include [2, 8, 14, 23–29]:
- *X-linked lymphoproliferative syndrome-XPL (Duncan's disease).* Characterized by an uncontrolled increase in the number of cytotoxic T and NK lymphocytes, the activity of which is directed against normal cells of various *organs.*
- *Post-transplant lymphoproliferative disorders (PTLD).* A heterogeneous group of diseases caused by uncontrolled proliferation of the lymphatic system cells, most frequently B cells (90%), less frequently T cells (9%) and NK cells (0.5%). In the case of EBV-seronegative recipients, the risk ranges from 23 – 50%, while in the case of EBV-seropositive recipients from 0.7 – 1.9%. The mortality rate in the course of PTLD is 40 – 80% in the flesh recipient, whereas in the case of bone marrow transplant it can reach 90.
- *Leukoplakia hairy mouth.* A mild proliferative change in epithelial cells which most frequently affects people infected with HIV. Characterized by changes on the tongue and in the nasopharynx.
- *Burkitt's lymphoma.* A rapidly growing malignant tumour composed of large B-type lymphoblasts. It mainly affects facial bones-mandible and the jaw.
- *Hodgkin's lymphoma (HL).* A proliferative disease of the lymphatic system. Its peak incidence occurs between 20 – 30 years of age, next after 50 years of age, and slightly more frequently affects men. It starts with changes in the lymph nodes (usually the neck and the supraclavicular area) and gradually occupies other nodes and organs. The risk of developing HL is four times higher in the case of people who have had an EBV infection, compared to the general population risk.
- *Nasopharyngeal carcinoma (NPC).* Cancer of the nasal part of the throat. This is one of the most malignant tumours, both in terms of the histological structure and the clinical course. Metastases to regional lymph nodes occur early.

Head and neck cancer. This refers to a group of cancers located in the digestive tract (including cancer of the lips, oral cavity, nasal cavity, paranasal sinuses, pharynx and larynx, oesophagus and adrenal glands, salivary glands and localized glands lymph nodes). About 90% of cases of head and neck cancer are squamous carcinoma. Squamous cell carcinoma of the head and neck (HNSCC) originates from the mucosal lining, causing tumour development in the nasal cavity and mouth, nasopharynx, larynx, esophagus, erosion and paranasal sinuses [30]. Although many potential risk factors of head and neck cancers have been identified, including smoking and chewing tobacco, alcohol consumption, poor diet combined with a hypodynamic lifestyle, acid reflux disease, haematopoetic stem cell transplantation, ionizing radiation, electromagnetic fields, and exposure to carcinogenic chemicals, various pathogenic infections also constitute an underestimated but significant risk. The International Agency for Research on Cancer (IARC) estimates that in 2008, 16% of total new cases of cancer and 20% of deaths caused by cancer worldwide were due to infections [30].

Nasopharyngeal carcinoma. Nasopharyngeal carcinoma (NPC) is a cancer of nasopharyngeal epithelial cells [11]. It is a cancer rarely found in Western countries, mainly in the countries of South-East Asia and North Africa, particularly in southern China, Singapore, Malaysia and northeastern India. Most of the NPC neoplasms are associated with EBV infection. It occurs mainly in middle-aged men and more commonly in men than women [31]. According to the WHO, there are three types of NPCs: squamous cell carcinoma, non-Hodgkin's, and non-differentiated cancer. The EBV infection is mainly related to types 2 and 3, whereas for the first type one can find both studies which confirm and which do not confirm the presence of the EBV [12]. There are three main etiologic factors in NPC development: genetic predisposition, chemical carcinogens and the EBV infection. The relationship between EBV and NPC was reported in 1973. IARC classified the EBV virus into the first group of carcinogens due to that dependence [32, 33]. In 100% of cases of nasopharyngeal carcinoma, the presence of the EBV is identified [11]. In the current research, EBV was identified in 57.5% of patients, including 60% of laryngeal carcinomas and 53.3% of oropharyngeal carcinomas [34]. Data provided in the literature suggests that the role of EBV in OSCC depends on the geographical region [35]. South-east Asian studies found a high prevalence of EBV and a conclusion was made on the etiological role of EBV in OSCC. North American studies, as well as West and North-European

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studies, describe a lower prevalence of EBV and conclude that the role of EBV in OSCC is questionable. Jalouli et al. received tissue samples obtained from patients with oral cancer from eight different countries and they indicated the highest overall EBV prevalence of 55% (ranging from 22% in Yemen to 80% in the UK [27, 28].

Gastric cancer. In 1990 Burke et al. [36] for the first time described the relationship between the EBV infection and gastric cancer. This tumour is called Epstein-Barr Virus-Associated Gastric Carcinoma (EBVaGC). In 1976, Zur Hausen [37] described the relationship between EBV infection and carcinogenesis, and in 2004 the role of EBV in gastric cancer [38]. EBVaGC is defined as monoclonal proliferation of cancerous cells latently infected with this virus [39]. Globally, the incidence of EBV infection in gastric cancer varies from 2 – 20%, on average about 10%. The differences are due to geographical and environmental factors. It is estimated that annually approximately 70,000 – 80,000 people develop EBV-associated gastric cancer. According to a meta-analysis conducted by Murphy et al. [40], EBVaGC incidence is 9.9% in North America, 9.2% in Europe, and 8.3% in Asia (i.e. 8.7%, on average). Camargo et al. [41] performed a similar analysis and obtained higher results, i.e. North America – 12.5%, Europe – 13.9%, and the lowest result in Asia – 7.5%. Approximately 90% of the world population is infected with the EBV, but only some individuals develop EBV-associated cancers, including gastric cancer (95% of gastric cancer cases are adenocarcinoma). The EBV infection can lead to chronic gastritis and carcinogenesis [42]. More than 950,000 cases of gastric adenocarcinoma are diagnosed in the world, and the relationship with the EBV is estimated to be around 10%. Annually 84,000 of these EBV infections are diagnosed worldwide [43]. Gastric cancer is the third leading cause of cancer deaths in the world. Only in 2012, 723,000 deaths were recorded. According to data published in *Nature* [34], in 2012 in Poland EBV positive gastric cancer accounted for 12.5%. For a virus to be regarded a cancer etiological factor, certain conditions must be met, i.e. there must be a causal link between the occurrence of the virus and the tumor, the presence of antigen or virus genome in cancerous cells must be established, the virus must be isolated from the cancerous tissue and be capable of *in vitro* cell transformation. The Epstein-Barr virus meets all of the above criteria. [31].

The number of studies and publications on various aspects of gastric cancer is steadily increasing. According to a meta-analysis by Chen et al. [30], at the PubMed database at the end of September 2014, there were more than 600 publications on the association of EBV infection with the development of gastric cancer. Meta-regression analysis is discussed in a further 39 articles published after 2014 [44]. EBV + is the largest group of cancer associated with this infection. EBVaGC is defined by the presence of the virus in cancerous cells. A meta-analysis of 9,738 cases (48 studies) estimated EBV positive at 8.8% [45]. EBVaGC is more common in younger patients, i.e. between 50 – 68 years of age, while the EBV is more frequently found in older patients, between 56 -72 years of age. It is also more common in men from Caucasian and Hispanic ethnic groups. Correlations with patients' age were not found, whereas cigarette smoking is a recognized risk factor. [46, 47]. In their own research, 62.5% of the total were male, and over 40% were more than 60 years old. Most of them (70%) were cigarette smokers. According to the Cancer Atlas Research Network of 2014,

gastric cancer is divided into four molecular types: gastric cancer positive for EBV, microsatelite instability, genomically stable and chromosomal instability. This division includes EBV infection as well as genetic and epigenetic changes [34]. Studies conducted in Japan showed a statistically higher EBVCA level among gastric cancer patients (34.7%) than in the control group (2.3%) [39]. On the other hand, Shinkura et al. [48] and Kayamba et al. [49] showed a higher titre of anti-EA antibodies in EBV positive patients. This could suggest reactivation of infection in early stages of cancer transformation. The level of anti-EA antibodies was statistically higher in patients than in the control group (29% vs. 8.6%). Therefore, it is believed that the EBV may be involved in the early stages of gastric cancer development [50]. According to Tsao et al. [13], LMP1 may play a different role in the early and late stages of carcinogenesis. Carcinogenesis may begin after the infection has passed into a state of permanent latency. High levels of LMP1 expression may lead to the disruption of the cytotoxic effect of cancerous cells, followed by an increased frequency of mutation and methylation in EBVaGC. The authors of this theory, however, are aware of the need for further research that would confirm these assumptions [13].

CONCLUSION

The Epstein-Barr virus effectively and permanently infects over 95% of the human population. In some infected people, under certain conditions, EBV can affect the development of serious diseases such as cancer. A considerable number studies suggest that EBV contributes to cell proliferation and survival, and may directly contribute to the development of EBVaGC through these effects. EBV affects multiple host proteins and pathways that normally promote apoptosis and regulate cell proliferation. Despite knowledge about the life cycle of EBV and the function of many viral proteins, the mechanism of neoplastic transformation remains unexplained. There is still no direct evidence of the influence of EBV infection on the induction of many cancers.

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