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FEATURES OF THE RELATIONSHIP OF THE EPSTEIN-BARR VIRUS AND THE HUMAN ORGANISM IN THE DEVELOPMENT OF LYMPHOPROLIFERATIVE DISEASES

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SUMMARY

The role of the virus in the induction of carcinogenesis is still not fully understood. It can participate in genetic alterations of lymphocytes, leading to malignant transformation of these cells, and contribute to immunodeficiency states, against the background of which there is an increased proliferation of neoplasm. There is no direct relationship between the already developed oncopathology in conditions of virus association and the worst outcome of the disease, however, antiviral prophylaxis has a positive effect on the course of lymphoma treatment.

An analysis of the current literature shows that despite a sufficient amount of clinical material regarding virus-associated non-Hodgkin's lymphomas (NHL), many questions remain unresolved. Such as, what is the molecular biological signaling of the development of NHL under viral load? What is the role of modern molecular genetic markers of lymphoma virus-association in the diagnosis and tactics of treatment of NHL? What are the morphofunctional and immunobiological factors for predicting the course of virus-associated NHL?

The discovery made in 1964 by Antony Epstein (Antony Epstein) and Yvonne Barr, marked a new era in clinical and experimental oncology.[1,5,9,12] The subject of their discovery was the first human oncogenic virus, named later by the names of the authors - Epstein-Barr virus (EBV).[2,4] Despite the more than 45-year period of studying the biological properties of this virus, carried out in numerous laboratories in the world, EBV still remains a mystery virus.[3,4,6,8,10] On the one hand, it is a ubiquitous virus that almost totally infects the population of the Earth, on the other hand, it is a proven or suspected etiological agent for a number of benign and malignant neoplasms of lymphoid and epithelial origin.[4,7,9,11] The most convincing argument in favor of EBV carcinogenicity is the discovery in the malignant cells of the genetic information of the virus caused by tumors in the form of extrachromosomal clonal episomes.[2,6,9,10] The clonality of the virus suggests the development of events according to which a tumor arises from a single EBV-infected cell, whose successful further selection can be stimulated by the expression of one or several viral genes.[4,8] This assumption is supported by the ability of EBV to "immortalize" ("immortalize") human B lymphocytes in vitro and the ease of spontaneous establishment of EBV-containing lymphoblastoid cell lines (LCL) from blood samples and lymphoid tissue of persons infected with the virus, especially in cases of host immunosuppression.[5,9,10,11,14] However, the carcinogenicity of EBV is far from unequivocal.[8,10] Despite the fact that the products encoded by the virus can cause the proliferation of infected cells, leading to the occurrence of lymphomas in immunocompromised patients, these clinically aggressive tumors are often polyclonal and regress when the immune response to EBV is restored.[9,10,14] Such tumors as Burkitt's lymphoma (LB), Hodgkin's lymphoma (LH), are found not only in VEB-associated, but also in VEB-unassociated variants, which suggests that the pathogenesis of these tumors is associated not only with VEB.[12,14] In addition, the malignant cells of patients with LB and LH differ phenotypically from LAL cells obtained under the influence of EBV in vitro and do not express a number of proteins necessary for transforming growth.[5,12] These findings suggest that tumor cells may also arise under the influence of factors of non-viral origin, as well as depend on various stimuli that enhance cell growth.[2,8,13,15]

It is proved that Epstein — Barr virus (EBV) serves as an etiological agent for many human malignant neoplasms, including tumors of lymphoid, epithelial and mesenchymal origin.[5,12,14,15] Tumors of lymphoid origin are characterized by heterogeneity of morphological and molecular characteristics, as well as clinical course.[6,7,9,13,15] At the same time, non-Hodgkin's lymphomas (NHL) account for about 70% of all

malignant lymphomas, and Hodgkin's lymphoma (LH) - the remaining 30%. For LH, on the basis of epidemiological observations and morphological data, the infectious nature and the presence of a small number of clinical options have long been suggested.[6,9,11,14] The desire to understand the etiology of NHL was complicated by their heterogeneous composition, numerous clinical manifestations and differing histopathological and immunological phenotypes.[5,8,10,12] Several attempts have been made to create an appropriate classification for lymphoid neoplasms.[5] The last classification for hematopoietic and lymphoid tissue tumors was proposed by WHO in 2008.[6,9]

The purpose of this review is to review current understanding of the role of EBV in the pathogenesis of EBV-associated hemoblastosis, as well as to present the latest developments in immunotherapeutic strategies that suggest new approaches for the effective treatment of these tumors.

Subsequent in-depth studies, including serology, allowed VEB to be identified as a new representative of the herpesvirus family.[4,9] Due to serological studies, it can also be assumed that EBV is the etiological agent of infectious mononucleosis (MI) and, besides LB, is closely associated with the undifferentiated histological variant of nasopharyngeal cancer (PHN).[11,15] In the following years, the contribution of EBV to the pathogenesis of LB, RNG, as well as certain variants of LH, NHL, T- and NK-cell lymphomas and gastric cancer (RJ) was actively studied.[7,9,11] EBV is a member of the rep-herpesvirus family of the lymphocryptovirus genus.[4,10] In the classification based on the taxonomy of herpetic viruses, EBV is also referred to as herpes virus type 4 (human herpes virus 4, HHV4).[6] The EBV genome is a double helix of DNA with a length of about 172 thousand base pairs.[8] Virionic DNA is linear.[9] In infected cells, viral DNA is usually not integrated into the cellular genome, but is extrachromosomally located in the nucleus in the form of a closed ring (episome), which is formed as a result of circularization of the viral genome through its terminal repeats (TR).[11,14] The biological significance of the integration of EBV into the cell genome remains unclear.[5] It has been suggested that episomal DNA is necessary for the realization of full-fledged EBV replication, culminating in the formation of viral particles.[9] A characteristic feature of the EBV genome is the presence of a large number of repeats in it, which differ in different strains of the virus and determine the structural and functional diversity of a number of proteins encoded by the virus.[8,15] Studies have shown that EBV infects a person in childhood, then persisting in the host's organism throughout its life. Infection is usually asymptomatic.[6] The constant presence of EBV in the human body becomes possible only due to latent infection of the fraction of circulating memory B-cells. In these cells, the expression of viral genes is significantly restricted by non-coding viral RNA (EBER) and right-handed BamA transcript (BART) RNA.[2,4] At the same time, the expression of other genes in memory B cells is absent.[10,11] This type of latency is sometimes referred to as late type 0, which allows the virus to avoid an immune response from the body.[8,12] Type I latency is characterized by the expression of EBV-encoded RNA (EBER-1 and EBER-2, as well as BART), supplemented by expression of the nuclear antigen of type 1 virus, EBNA-1.[6,9] In this case, the expression of other latent proteins is not observed. This type of latency is characteristic of LB cells. Type II latency is characteristic of tumor cells of the RNG, as well as EBV-associated cases of HL and RJ.[4] In addition to the expression of the above mentioned viral RNA (EBER, BART) and EBNA-1, this type of latency is also observed. Currently, many researchers believe that EBV's contribution to carcinogenesis is due to its ability to cause genetic and epigenetic changes that can stimulate cell growth or indirectly, by inhibiting apoptosis or protecting tumor cells from the influence exerted on them by the microenvironment and the host immune response.[7] An attempt to understand the complex relationship between EBV and the body in various lymphoproliferative diseases of humans is devoted to this review.

In the WHO-classification of Hematopoietic and Lymphoid Tumors, malignant lymphomas are assigned to a separate group, within which they can be divided according to morphological, immunophenotypic, and biological features.[4,11] Groups of lymphomas have a clear epidemiology, clinical signs and often a very special response to therapy.[7,9] Such differences are often explained by the biology of lymphomas, for example, the frequency of cell division of lymphoma (as opposed to apoptosis), activation of oncogenes, loss of influence of suppressor genes, presence of chimeric genes, development of multidrug resistance, particular cell microenvironment and association with infectious agents of the NHL variant; treatment of relapses and resistant forms.[12]

Currently, it has been proved that about 20% of all human tumors are induced by viruses or develop with their active participation.[1,4] The number of lymphoma-associated viruses has increased over the past 20 years and includes Epstein-Barr virus (Epstein-Barrvirus, EBV, EBV), T-cell lymphotropic human virus 1 (Human T-celllymphotropicvirus 1, HTLV1), human immunodeficiency virus (Humanimmunodeficiencyvirus, HIV1 and 2) and human herpes virus type 8 (Humanherpesvirus, HHV8).[10] Some of them cause the development of lymphomas by direct oncogenesis (EBV and Burkitt's lymphoma).[12] Others induce lymphomas in immunosuppressed patients (for example, HHV8). Lymphomas in patients with HIV are due to the direct effect of the virus on lymphocytes, as well as the development of acquired immunodeficiency syndrome. Moreover, 50% of these lymphomas are caused by EBV infection. Effective treatment of virus-associated lymphomas is often quite difficult due to the aggressive

nature and course of the disease (for example, Berkitt's lymphoma), as well as inadequate dose regimen or the development of infection during chemotherapy in patients who are already in a state of immunosuppression.[9]

Understanding the mechanism of virus induction of malignant pathologies is assisted by observations and clinical studies that demonstrate the association of an increased risk of cancer with primary or acquired immunodeficiencies, autoimmune diseases, and the use of immunotherapy to treat chronic inflammation (for example, an autoimmune nature) or therapeutic support for organ transplantation.[9,13]

Understanding the relationship between immune status impaired by viral contamination of the body and the risk of developing cancer is usually based on a comparison of two paradigms: the immune system protects the body by observing the appearance of tumor cells and oncogenic viruses (an example of an immune model of carcinogenesis) and chronic inflammation can increase tumor growth and metastasis (inflammatory model).[9] While these models support the role of the immune status in many types of cancer pathologies, they are insufficient to explain the disproportionate increase in the risk of B-cell lymphoma in a population of patients with chronic immunosuppression or inflammation. For example, the presence of the Epstein-Barr virus (EBV) in patients with lymphomas demonstrates the variable role of the virus in lymphomagenesis.[13] Evaluation of DNA variations found in tumor cells and an understanding of B-cell ontogenesis gives an idea of the extremely high sensitivity of lymphocytes, mainly B-cells, to tumor transformation.[12] Thus, the infection of the human body with the HIV viruses, Epstein-Barr, herpes type 8, hepatitis B and C provokes the emergence and development of malignant lymphomas.

Epstein-Barr virus (EBV) serves as an etiological agent for many human malignant neoplasms, including tumors of lymphoid, epithelial and mesenchymal origin. Tumors of lymphoid origin are characterized by heterogeneity of morphological and molecular characteristics, as well as clinical course.[9] At the same time, non-Hodgkin's lymphomas (NHL) account for about 70% of all malignant lymphomas, and Hodgkin's lymphoma (LH) - the remaining 30%. For LH, on the basis of epidemiological observations and morphological data, infectious nature and the presence of a small number of clinical options have long been assumed. The desire to understand the etiology of NHL was complicated by their heterogeneous composition, numerous clinical manifestations and differing histopathological and immunological phenotypes. Several attempts have been made to create an appropriate classification for neoplasms of a lymphoid nature.

Non-Hodgkin lymphoma (NHL) is a collection of neoplasms in the occurrence of which various agents are involved. These agents, depending on the mechanism of their action, can be assigned to three different groups.[12] The first group is viruses that transform lymphocytes and other cells (EBV, HHV-8). The second group is represented by factors of different nature, causing immunodeficiency states. These factors primarily include (not counting the hereditary damage to the immune system) of HIV. This virus causes immunosuppression in an infected person as a result of depletion of the CD4 + T-lymphocyte pool and the onset of AIDS. In turn, AIDS appears to be a significant risk factor for some types of lymphomas, including, in particular, the high degree of malignancy of B-cell NHL. The third group includes some infections (for example, H. pylori), which increase the risk of occurrence of NHL against the background of the chronic stimulation of the immune system and the constant activation of lymphocytes caused by them. NHL morphological and molecular characteristics, as well as the clinical course are heterogeneous lymphoid tumors, constituting up to 90% of all malignant lymphomas.[10] These tumors, with a few exceptions, have B-or T-cell origin, and their heterogeneity, at least in part, is due to many stages of normal differentiation and maturation of these cells.[3,6] Currently, according to the WHO classification adopted in 2008, there are 36 tumor variants among the NHL: 21 - B-cell origin and 15 - T-cell (excluding neoplasms of unknown origin). According to this classification, chronic lymphocytic leukemia together with its non-leukemic variant (small lymphocytic lymphoma) belong to the NHL group. This group also includes plasma cell tumors.[5,11]

As already mentioned, EBV is a virus that transforms lymphocytes, and in addition to LH, he is involved in the emergence of several variants of NHL. A prominent representative of a B-cell tumor associated with EBV is LB. Currently, there are three variants of LB: endemic (affecting equatorial Africa and New Guinea), sporadic (in children and young people anywhere in the world) and immunodeficient (mainly associated with HIV infection).[12] The most typical clinical manifestation of the endemic LB is a lesion of the jaw bones and the facial part of the skull. Studies have shown that up to 95% of all tumors of this form of LB are associated with EBV, as evidenced by the presence of viral markers (viral RNA and DNA) in tumor cells.[10,13,14] In addition, in endemic regions, high titers of virus-specific antibodies that occur in children in the first years of life as a result of massive EBV infection increase the risk of LB tenfold and may precede the development of a tumor in months or even years.[12] The sporadic form of LB, occurring outside the endemic regions (in Europe, USA), is a rare tumor in children, is even less common in adults, usually affects the large intestine, and sometimes the ovary, kidneys or mammary glands. Despite the morphological similarity, this form of LB differs from the endemic low (5–15%) link with EBV.[7,9,13,14] Among HIV-associated (immunosuppressive) lymphomas, LB-like is about 40%. Their morphological, clinical, cytogenetic and molecular genetic characteristics

coincide with those of LB, not associated with HIV. The histological picture is typical enough for all forms of LB: large macrophages scattered among small lymphocytes with basophilic cytoplasm and a round-oval nucleus, create a picture of the so-called «starry sky». Tumor cells are monoclonal and contain one of the variants of reciprocal chromosomal translocations, most often between chromosome 8 and 14, but in about 10% of cases other variants of translocations are noted (2; 8 and 8; 22). In the process of translocation, the c-myc proto-oncogene located on chromosome 8 moves into the region of the genes encoding the immunoglobulin heavy chains, as well as the λ- and γ-light chains on chromosomes 14, 2 and 22 (85, 10 and 5% of cases, respectively). For other types of translocations (2; 8 and 8; 22), the c-myc remains on chromosome 8, but sections of the genes encoding immunoglobulins with chromosomes 2 and 22 are adjusted to it.[11,13] The placement of the regulatory elements of these loci adjacent to the c-myc proto-oncogene leads to an imbalance in the work of this gene, often increased expression of the proteins encoded by it and, ultimately, its acquisition of a transforming potential (the c-myc proto-oncogene turns into a c-myc oncogene). LB is characterized by type I EBV latency, characterized by the expression of a limited number of viral genes and the products encoded by them (EBER-1, EBER-2, and EBNA-1). Expression of an additional number of genes (EBNA-2, LMP-1 and BZLF-1) is observed only in rare tumor cells and, even more rarely, LB cells can enter a lytic cycle accompanied by the expression of a wide spectrum of viral genes.[3,5,11,12] In lymphoma cells, the expression of cellular genes (as well as viral) is significantly reduced, probably as a result of the inhibitory effect of viral proteins. Nevertheless, malignant cells constantly express such B-cell markers as CD19, CD20 and CD22, surface immunoglobulins, most often IgM, less often IgG and IgA. These cells are also characterized by a low level of expression of HLA class I antigens, cellular markers of activation and adhesion molecules[12], which allows a single protein among EBNA-1 virus markers to not be recognized as a target for recognition by EBV-activated cytotoxic lymphocytes. In this case, the expression of EBNA-1 in EBV-infected B-cells provides them with a selective advantage (compared to uninfected cells) and avoids the body's immune surveillance.[12] Since the virus is associated only with a certain part of cases of LB (about 90% in African countries and about 10% in European countries and the USA), its relation to chromosomal rearrangements in which the c-myc proto-oncogene participates is not completely clear, VEB in the occurrence of LB is still a mystery. The role of the virus is, apparently, only in the initiation of the process of transformation of B-lymphocytes. In endemic regions, VEB-induced lymphoproliferation is exacerbated by malaria infection[13], and outside endemic regions by other factors associated with immunosuppression (parasitemia, infectious diseases, including AIDS, immunosuppressive therapy in oncological patients or organ recipients, etc.). One of the effects of these factors is a high level of cytokines that stimulate B-cell proliferation.[5,12] Enhanced lymphoproliferation significantly increases the population of infected B-lymphocytes, in which there are chromosomal changes necessary for the formation of a tumor cell. On the other hand, it has recently been shown that EBNA-1 transactivates the genes involved in the rearrangement of the Ig gene, promotes genetic instability, and has some anti-apoptotic functions. Thus, EBV can make a definite contribution to genetic events leading to the occurrence of LB.[9,11] As for the role of c-myc, its activation as a result of chromosomal translocations leads to the suppression of cell aging processes, but makes them more susceptible to spontaneous or drug-induced apoptosis. EBV may counteract the apoptotic effect of c-myc-activated individual viral genes (EBER, EBNA-1, EBNA-LP), although the significance of these anti-apoptotic effects of the virus in the pathogenesis of LB remains unclear.[5,9] This is due to the fact that these viral products are either not expressed or expressed in a part of the tumors, and most importantly, the viral carriage does not replace the genetic inactivation of the main apoptotic signaling pathways. It is important to note that in LB cells, the signaling pathway associated with p53 is permanently inactivated in one way or another, that is, this event serves as an important part of the tumor process.[6,9] In fact, inactivation of the p53 signaling pathway occurs in most, if not all human tumors, but in cases of LB, there is no clear correlation between the inactivation of this gene or its mutation with the presence of EBV. The same is true for the Rb-signaling pathway, which can effectively interfere with uncontrolled proliferation through blocking the S-phase of the cell cycle. In LB cells, the signaling pathway of Rb is in most cases inactivated using the epigenetic mechanism, p16 hypermethylation or its damage is higher in the genome (upstream). Other options for inactivating this signaling pathway are also possible. In general, it can be assumed that mutations in the p53 and Rb signaling pathways accumulate much more easily in EBV-positive tumors than in EBV-negative tumors, which apparently determines the contribution of EBV to LB carcinogenesis.[4,6,10,14]

At the same time, the role of the virus in the induction of carcinogenesis is still not fully clarified: it can participate in genetic alterations of lymphocytes, leading to malignant transformation of these cells, and contribute to immunodeficiency states, against the background of which enhanced proliferation of neoplasms occurs. There is no direct relationship between the already developed oncopathology in conditions of virus association and the worst outcome of the disease, however, antiviral prophylaxis has a positive effect on the course of lymphoma treatment.[2,5,7,10]

Analysis of the current literature shows that, despite a sufficient amount of clinical material regarding virus-associated NHL, many questions remain unresolved:

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REFERENCES

1. Benharroch D., Einav I., Feldman A. et al. Apoptosis of Hodgkin-Reed-Sternberg cells in classical Hodgkin lymphoma revisited. APMIS, 2010; 118: 339-45.
2. Bornkamm G.W. Epstein-Barr virus and its role in the pathogenesis of Burkitt's lymphoma: an unresolved issue. Semin. Cancer Biol., 2009; 19: 351-65.
3. Baker P.S., Gold K.G., Lane K.A. et al. Orbital Burkitt lymphoma in immunocompetent patients: a report of 3 cases and a review of the literature. Ophthal. Plast. Reconstr. Surg., 2009; 25: 464-8.
4. Mueller N., Evans A, Harris N.L. et al. Hodgkin's disease and Epstein-Barr virus. Altered antibody pattern before diagnosis. N. Engl. J. Med., 1989; 320: 689-95.
5. Klein G., Klein E., Kashuba E. Interaction of Epstein-Barr virus (EBV) with human B-lymphocytes. Biochem. Biophys. Res. Commun, 2010; 396: 67-73.
6. Pai S., Khanna R. Role of LMP1 in immune control of EBV infection. Semin. Cancer Biol., 2001; 11: 455-60.
7. Thompson M.P., KurzrockR. Epstein-Barr virus and cancer. Clin. Cancer Res., 2004; 10: 803-21.
8. Timms J.M., Bell A, Flavell J.R. et al. Target cells of Epstein-Barr-virus (EBV)-positive post-transplant lymphoproliferative disease: similarities to EBV-positive Hodgkin's lymphoma. Lancet, 2003; 361: 217-23.
9. Pittaluga S., Wilson W.H., Jaffe E.S. Lymphomatoid granulomatosis. In: WHO Classification of Tumors of Haematopoietic ans Lymphoid Tissues. Ed. by S.H. Swerdlow, E. Campo et al. Lyon: IARC-press, 2008: 247-9.
10. Raphael M., Said J., Borisch B., Cesarman E., Harris N.L. Lymphomas associated with HIV infection. In: WHO Classification of Tumors of Haematopoietic and Lymphoid Tissues. Ed. by S.H. Swerdlow, E. Campo et al. Lyon: IARC-press, 2008: 340-2.
11. Said J., Cesarman E. Primary effusion lymphoma. In: WHO Classification of Tumors of Haematopoietic and Lymphoid Tissues. Ed. by S.H. Swerdlow, E. Campo et al. Lyon: IARC-press, 2008: 260-1.
12. Szekely L., Chen F., Teramoto N. et al. Restricted expression of Epstein-Barr virus (EBV)-encoded, growth transformation-associated antigens in an EBV- and human herpesvirus type 8-carrying body cavity lymphoma line. J. Gen. Virol, 1998; 79(6): 1445-52.
13. Stein H., Warnke R.A., Chan W.C., Jaffe E.S. Diffuse large B-cell lymphoma, not otherwise specified. In: WHO Classification of Tumors of Haematopoietic and Lymphoid Tissues. Ed. by S.H. Swerdlow, E. Campo et al. Lyon: IARC-press, 2008: 233-7.
14. Shimoyama Y, Asano N., Kojima M. et al. Age-related EBV-associated B-cell lymphoproliferative disorders: diagnostic approach to a newly recognized clinicopathological entity. Pathol. Int., 2009; 59: 835-43.
15. Wong H.H., Wang J. Epstein-Barr virus positive diffuse large B-cell lymphoma of the elderly. Leuk. Lymphoma, 2009; 50: 335-40.