Epstein-Barr Virus–Associated Lymphomas

Ewelina Grywalska and Jacek Rolinski

The Epstein-Barr virus (EBV) is the first identified human virus with a proven association with the pathogenesis of cancer. To maintain the integrity of the viral genome and to "get out" of the control of the host immune system, in the phase of the latent infection EBV shows the expression of several genes, including genes for six nuclear antigens, three latent membrane proteins, two short non-coding RNAs, and *BamHI-A* rightward transcripts. The different patterns of expression of these latent genes determine the occurrence of different types of latency in the pathogenesis of particular malignancies. One of the most important features of EBV is its ability to infect various cell types and the consequent variety of diseases. It has been shown that in humans, EBV infection may lead to the development of cancers, including those derived from hematopoietic cells. Although cases of T-cell and epithelial cell infections have been documented, EBV is characterized mainly by tropism for B lymphocytes, and under certain conditions their infection may result in transformation to B-cell lymphoma. This article discusses the mechanisms leading to the development of EBV-dependent lymphomas, and briefly characterizes these diseases.
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The Epstein-Barr virus (EBV; human herpesvirus 4, HHV-4) is the first human virus identified with a proven association with the pathogenesis of cancer. It belongs to the *Herpesviridae* family, subfamily *Gammaherpesvirinae*, genus *Lymphocryptovirus*.[1] Although the *Herpesviridae* family consists of more than 100 different viruses, it has been demonstrated so far that only the following of them are pathogenic for humans: herpes simplex virus 1 (HSV-1; also known as human herpesvirus 1, HHV-1), herpes simplex virus 2 (HSV-2; also known as human herpesvirus 2, HHV-2), varicella zoster virus (VZV; also known as human herpesvirus 3, HHV-3), cytomegalovirus (CMV; also known as human herpesvirus 5, HHV-5), human herpesvirus 6 (HHV-6), human herpesvirus 7 (HHV-7), Kaposi sarcoma–associated herpesvirus (KSHV; also known as human herpesvirus 8, HHV-8) and, as discussed here, EBV.[2]

Department of Clinical Immunology and Immunotherapy, Medical University of Lublin, Poland.
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Address correspondence to Ewelina Grywalska, MD, PhD, Department of Clinical Immunology and Immunotherapy, Medical University of Lublin, 4a Chodzki St., 20-093 Lublin, Poland. E-mail: ewelina.grywalska@gmail.com
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CHARACTERISTICS OF THE VIRUS IN THE CONTEXT OF PROLIFERATIVE HEMATOLOGICAL DISEASES

EBV can infect both B cells and epithelial cells, and transient reactivation of infection and viral replication in epithelial cells of the nasopharynx allows its spread in the body and latent infection of B lymphocytes.[3,4]

In order to maintain the integrity of the viral genome and to "get out" of the control of the host immune system, in the phase of the latent infection EBV shows the expression of several genes, including genes for six EBV nuclear antigens (EBNA-1, -2, -3A , -3B, and 3C, and EBV nuclear antigen–leader protein, EBNA-LP), three EBV latent membrane proteins (LMP-1, -2A, and -2B), two short non-coding RNAs (EBV-encoded small RNA, EBER-1 and -2), and *BamHI-A* rightward transcripts (BART).[3–6] The different patterns of expression of the mentioned latent genes determine the occurrence of different types of latency in the pathogenesis of particular cancers.[7]

In type I latency EBNA-1 expression dominates; it is observed in the course of Burkitt lymphoma (BL) and stomach cancer.[8–10] Type II latency is characterized by the expression of latent genes EBNA-1 and LMP-1 and LMP-2. It occurs in the course of Hodgkin lymphoma (HL), nasopharyngeal carcinoma (NPC), and in the state of heavy hyperinflammation in the form of hemophagocytic lymphohistiocytosis.[5,11–13]

In type III latency, expression of all the latent antigens is seen. This type of latency occurs in the course of post-transplant lymphoproliferative disorders (PTLD) associated with EBV infection, in AIDS-related lymphomas, and in lymphoblastoid cell lines (LCL).[6,7,14] In vitro, EBV can infect primary B cells, which are transformed into continuously proliferating LCL. It has been shown that in this process four latent viral antigens, EBNA-2, -3A, and -3C and LMP-1, are necessary.

One of the most important features of EBV is its ability to infect various cell types, and the variety of consequent diseases.[15] It has been shown that in human EBVs, infection may lead to the development of a variety of cancers, including those derived from hematopoietic and epithelial cells. Carcinogenesis occurs mostly in transplant patients and in patients with AIDS.[16,17] Although cases of T-cell and epithelial cell infection have been documented, EBV is characterized mainly by tropism for B lymphocytes; under certain conditions their infection may result in transformation to B-cell lymphoma.[18]

Due to the preferential infection of B cells, the most common forms of EBV-associated lymphoproliferative disorders are B-cell lymphomas: HL, non-Hodgkin lymphomas (NHLs), including BL and diffuse large B-cell lymphoma (DLBCL).[18–21] PTLD also develops as a result of EBV infection. Due to the still lengthening list of human cancers resulting from EBV infection, in 1997 the World Health Organization (WHO) classified EBV as a tumor virus.[22]

The function of latent EBV antigens has been and still is the subject of intense research since an undeniable link between the incidence of lymphoproliferative disorders developing after EBV infection and the presence of latent viral infection has been noticed. Information on the life cycle of EBV, its gene expression regulation and molecular mechanisms of malignant transformation may be essential for a complete understanding of the role of this viral infection in the course of a number of lymphoproliferative diseases and to develop new methods of treatment. According to current knowledge, latent antigens encoded by EBV interfere with a number of important cellular pathways, thereby leading to tumorigenesis.[6,23,24]

The main biological functions of latent proteins are summarized in Table 1.

THE ROLE OF LATENT ANTIGENS IN LYMPHOCYTE TRANSFORMATION

EBNA-1 is required for replication and maintenance of EBV episomes in dividing host cells. This protein is the only EBV-encoded antigen whose constitutive expression is found in all cancers associated with infection by the virus.[25,26] EBNA-1 has two main functional domains: the C-terminal domain binding viral DNA and the N-terminal domain tethering to the genetic material of the host cell.[27] Increasing evidence indicates that EBNA-1 plays a role in the progression of human tumors resulting from EBV infection. For example, reduction of EBNA-1 expression by RNA interference results in a reduction of proliferation and survival rates of a number of EBV-positive tumor cells.[28,29] These observations are confirmed by the fact that the increased expression of a dominant negative mutant variant of EBNA-1 is associated with enhanced EBV-positive BL cell death. This may indicate the anti-apoptotic effect of EBNA-1.[28,30] EBNA-1 expression also is associated with increased risk of metastasis in mice in which the tumor suppressor protein Nm23–^{1}H function has been blocked.[31] An anti-apoptotic effect of EBNA-1 also can be a consequence of the interaction of the protein with herpesvirus-associated ubiquitin-specific protease (HAUSP), present in the host cell.[32] In response to DNA damage, HAUSP interacts with p53, causing its stabilization. However, in cells infected by EBV, EBNA-1 can effectively block the interaction between HAUSP and p53, which results in degradation of the latter, controlled by the ubiquitin-proteasome system.[32] In addition, this protein can damage promyelocytic leukemia bodies (PML) in NPC cells and lead to genomic instability by "switching on" recombination activating genes *RAG-1* and *RAG-2*.[26,33] Although for a long time it was thought that cells expressing EBNA-1 are able to evade the cellular response of the immune system due to blockage of the presentation of antigens by major histocompatibility complex (MHC) class I molecules, it recently has been shown that the EBNA-1 protein can be displayed to both $CD4^{+}$ and $CD8^{+}$ T lymphocytes. This creates the possibility of using this protein as a potential target for immunotherapy of cancers developing as a result of EBV infection.[3,34,35]

EBNA-2 plays a key role in immortalization of the host cells, controlled by the EBV, coordinating the level of transcription of the viral genes and several cellular genes.[13] EBNA-2 alters the activity of the host cell genes, including genes encoding the B-cell activation markers CD21 and CD23, and the transcription factors.[36,37] Based on the significant differences in the sequence, two serologically different EBNA-2 proteins were identified, specific to type 1 and 2 EBV. This structural diversity is also reflected in the EBNA-2 impact on B-cell transformation in vitro.[4] Although in vitro studies have shown that EBNA-2 is essential for the initial stages of the transformation of EBV-infected B lymphocytes, its expression may be less important during tumor progression. Observations made on the majority of