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Review

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Epstein-Barr virus-associated lymphoproliferative disorders*

Choroby limfoproliferacyjne związane z zakażeniem wirusem Epsteina-Barr

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Summary

The Epstein–Barr virus (EBV) is one of the most common human viruses, infecting more than 90% of the world's adult population. In some individuals the interplay between EBV replication, latency and immune control can be disrupted and evokes prolonged proliferation of EBV-infected lymphocytes and their malignant transformation. Since its discovery as the first human tumor virus, EBV has been implicated in the development of a wide range of human cancers. The evidence for an association with EBV is the strongest for Burkitt's lymphoma, NK/T cell lymphoma, nasopharyngeal carcinoma, Hodgkin's lymphoma and for malignant lymphomas in immune incompetent patients. Additionally, certain epithelial cell tumors, such as gastric carcinoma and breast carcinoma, have been defined as EBV related. However, the virus may be encountered in other types of malignancies. The oncogenic potential of EBV is related to its ability to infect and transform B lymphocytes into continuously growing lymphoblastoid cell lines. EBV encodes a series of products mimicking several growth, transcription and anti-apoptotic factors, to usurp control of the pathways that regulate diverse homeostatic cellular functions. However, the exact mechanism by which EBV promotes oncogenesis remains unclear. The focus of this review is to summarize the current knowledge of oncogenic potential of the Epstein–Barr virus and its role in the pathogenesis of EBV-associated lymphoproliferative disorders.

Keywords: EBV • lymphoma • lymphoproliferative disorder • oncogenesis • tumor

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List of abbreviations:

Ag – antigen; **AID –** activation-induced cytidine deaminase; **AIDS –** acquired immune deficiency syndrome; **AITL** – angioimmunoblastic T-cell lymphoma; **APC –** antigen-presenting cell; **BCR –** B-cell receptor; **BL –** Burkitt's lymphoma; **CAEBV –** chronic active Epstein-Barr virus disease; **CD –** cluster of differentiation; **CD40L** – CD40 ligand; **CMV** – cytomegalovirus; **CTL** – cytotoxic T lymphocyte; **DC** – dendritic cell; **DLBCL** – diffuse large B-cell lymphoma; **EA** – early antigen; **EBERs** – *EBV*-encoded small RNAs; **EBNA** – *Epstein-Barr nuclear antigen*; **EBV** – Epstein-Barr virus; **GC** – germinal center; **HHV** – human herpes virus; **HIV** – human immunodeficiency virus; **HL** – Hodgkin's lymphoma; **HLA** – human leukocyte antigens; **HRS** – Hodgkin and Reed-Sternberg cells; **HSV** – herpes simplex virus; **HSCT** – hematopoietic stem cell transplantation; **HTLV-1** – human T-cell leukemia virus-1; **IFN** – interferon; **Ig** – immunoglobulin; **IL** – interleukin; **KSHV** – Kaposi's sarcoma herpes virus; **LCL** – lymphoblastoid cell line; **LD** – lymphocyte depleted; **LMP** – latent membrane protein; **LP** – lymphocyte predominant; **LPDs** – lymphoproliferative disorders; **MALT** – mucosa-associated lymphoid tissue; **MC** – mixed cellularity; **MHC** – major histocompatibility complex; **NHL** – non-Hodgkin's lymphoma; **NK** – natural killer; **NPC** – nasopharyngeal carcinoma; **NS** – nodular sclerosing; **PBMC** – peripheral blood mononuclear cells; **PCNSL** – primary central nervous system lymphoma; **PEL –** primary effusion lymphoma; **PLT** – platelets; **PTLD** – post-transplant lymphoproliferative disease; **RBC** – red blood cells; **RNA** – ribonucleic acid; **SCID** – severe combined immunodeficiency; **TAA** – tumor-associated antigens; **TCR** – T-cell receptor; **TGF** – transforming growth factor; **Th** – T helper; **TLR** – Toll-like receptor; **TNF** – tumor necrosis factor; **VCA** – viral capsid antigen

Introduction

Epstein-Barr virus (EBV), also called human herpes virus 4 (HHV-4), was the first human virus to be directly implicated in carcinogenesis. EBV is a part of the Herpesviridae family [99,117]. It was discovered by Michael Epstein and Yvonne Barr in 1964 during their research on Burkitt's lymphoma (BL) [32]. Since its discovery, EBV has been found in a variety of other tumor types. The evidence for an association with EBV is the strongest for BL, NK/T-cell lymphoma, nasopharyngeal carcinoma (NPC), Hodgkin's lymphoma (HL) and for malignant lymphomas in immune incompetent patients [47]. Additionally, certain epithelial cell tumors, such as gastric carcinoma [107] and breast carcinoma [5], have been found to be EBV related [78]. However, the virus may be encountered in other types of malignancies.

Like other members of the Herpesviridae, EBV virions have a double-stranded, linear DNA genome encoding approximately 100 genes surrounded by a protein capsid. A protein tegument lies between the capsid and the envelope. Mature virions are 120-180 nm in diameter. EBV infects more than 90% of the world's adult population. Infection usually occurs early in childhood. EBV infections are most prevalent in developing countries, in populations of low socioeconomic status [42, 116]. In countries with stringent hygiene practices, EBV seroprevalence tends to increase gradually with age, showing two seroconversion peaks: at 2 to 4 years and at 14 to 18 years [41]. The mean seroprevalence in children is approximately 50% and increases steadily to a value of 90% to 99% in adults [4].

There are two major strains of EBV (type 1 and type 2), differing in organization of the genes that encode the EBV nuclear antigen (EBNA) [90]. Both types are detected all over the world, with type 1 being the most frequent, although in some regions (e.g. central Africa, Papua New Guinea and Alaska) type 2 definitely predominates [37, 94]. The virus is passed to uninfected individuals with saliva or spread through close oral contact, but transmission by transfusion has also been documented [7].

In spite of frequent virus detection in latently infected blood donors, transmission of EBV infection by transfusion is thought to be relatively infrequent. This phenomenon could be explained by the fact that most adult recipients of blood and blood products are already immune to EBV. Moreover, blood from seropositive donors contains EBV-neutralizing antibodies and specific memory cells, which may protect the recipient from infection. Although we do not know exact EBV infectivity by blood and its components, it seems that the viral load in blood from healthy seropositive donors, which is normally low ($5/10^6$-$1/10^7$ peripheral blood mononuclear cells), is rather below an infection dose. In addition, it was established that the viability of B lymphocytes carrying the EBV genome may decline during blood storage. The risk of EBV transmission from red blood cell (RBC) and/or platelet (PLT) transfusions is also significantly reduced by leukoreduction. Thus, in most instances, EBV genomes contained in blood products should not cause severe disease when the transfused recipient is immune competent. However, whole blood and blood components as a potential source of infection should be kept in mind as an association between transfusion and EBV infection, especially in immunosuppressed young patients, is still being discussed [104].

Most primary EBV infections in normal individuals are unapparent, but occasionally EBV can cause acute infectious mononucleosis, which is a self-limited disease. Following primary EBV infection, individuals remain lifelong carriers of the virus. EBV then persists latently in the host

within long-life memory B cells [73]. The growth of B cells latently infected with EBV is normally controlled by the host immune response, particularly by virus-specific T cells [41]. However, in some individuals, the virus is implicated in the development of malignancy [25]. It is well documented that in the immunocompromised hosts, the interplay between EBV replication, latency and immune control can be disrupted and evokes prolonged proliferation of EBV-infected lymphocytes and their malignant transformation [17, 34]. There are hypotheses that there is an association between EBV infection and autoimmune [31, 111] and allergic diseases [61,97].

EBV can infect both B cells [9] and epithelial cells [100]. The role of epithelial cells in the life cycle of EBV is still incompletely defined. It is generally believed that epithelial cells in the oropharynx represent the site of primary EBV infection and replication [10]. This is followed by a latent infection of B lymphocytes. The B-lymphotropic nature of EBV is evidenced by the ability to immortalize normal resting B lymphocytes in vitro, converting them into permanently growing lymphoblastoid cell lines (LCL) [93]. EBV-infected B lymphocytes carry the viral genome in a latent form. In some circumstances, EBV latency may reactivate, resulting in the expression of viral genes encoding series of products stimulating anti-apoptotic molecules, cytokines, and signal transducers [77]. Disrupted control of the cellular pathways regulating a wide variety of homeostatic cellular functions leads to neoplastic transformation.

In healthy individuals, EBV is latently maintained in memory B cells, which express only the transcripts for EBV small RNAs (EBERs). This state is termed latency 0 and allows for persistence of the virus in a way that is nonpathogenic and not detectable by the immune system [103].

Three types of latent genes have been described (Figure 1). Type I latency, characterized by the expression of Epstein–Barr nuclear antigen 1 (EBNA-1) and two small noncoding Epstein–Barr RNAs (EBERs), was found in BL [19]. EBV gene expression in latency II, associated with classic HL and T-cell non-Hodgkin's lymphoma [91], is limited to EBNA-1, EBERs, latent membrane protein (LMP)-1, LMP-2A and LMP-2B. Latency III usually involves the unrestricted expression of all EBNAs, EBERs, and LMPs [22] and occurs mainly in immunocompromised individuals suffering from post-transplant lymphoproliferative disorders (PTLDs), HIV-associated lymphoproliferative disorders and in lymphoblastoid cell lines [117].

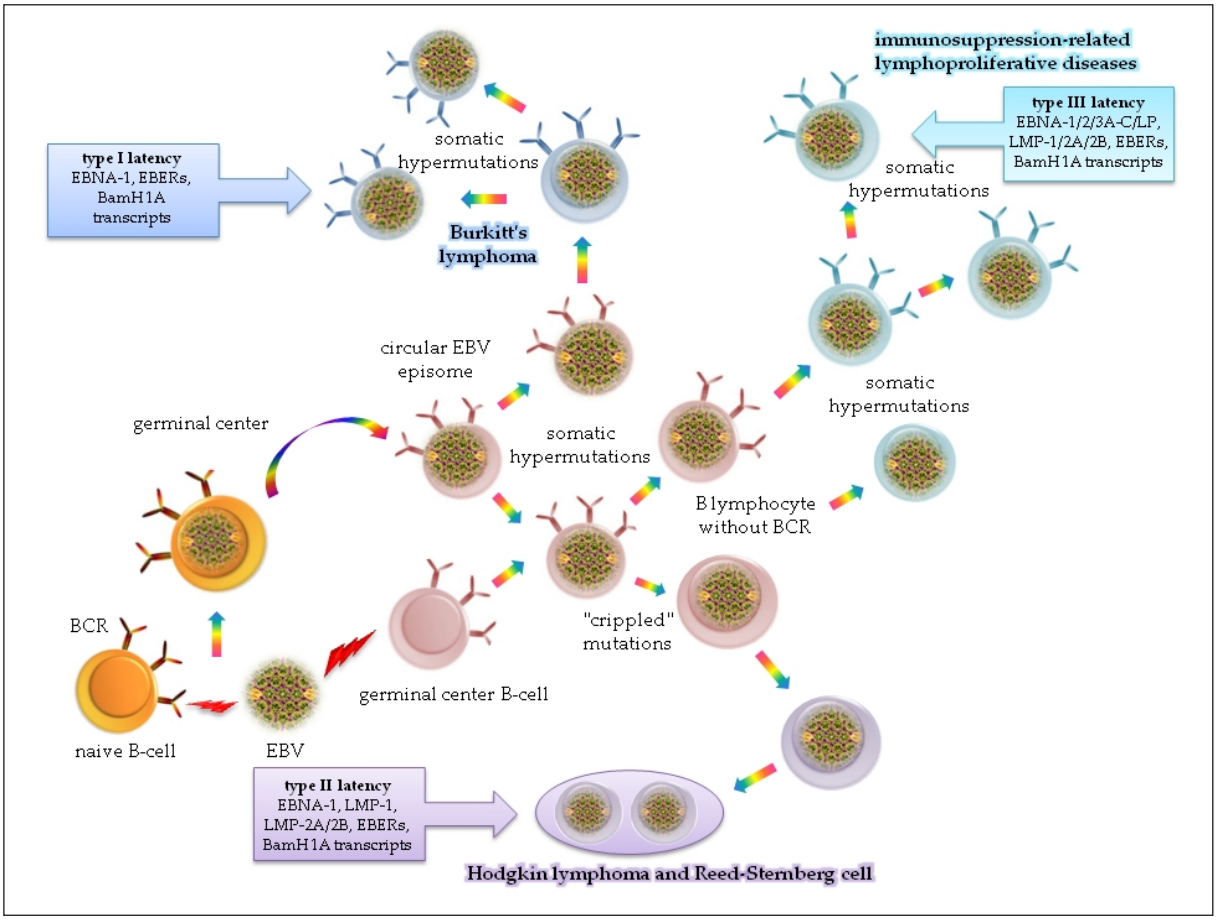

Fig. 1. Three forms of Epstein-Barr virus latency

The ability of EBV to efficiently transform B cells in culture to immortalized, transformed cells undoubtedly accentuates its connection to human cancers [83]. Although EBV may be essential for tumorigenesis, it is not generally sufficient on its own. Other factors such as specific failure of immune recognition, stimulation of B-cell proliferation by other infections, appearance of secondary genetic aberrations or mutations may also be important [99].

EBV usually infects B cells via the B-cell specific CD21 antigen [35] and EBV-associated hematologic malignancies are predominantly of B cell type. In addition, EBV is associated with rare T- and NK-cell malignancies [53,59]. EBV-positive lymphomas can be divided into those occurring in immunodeficient individuals, which are true virally driven lymphomas, such as PTLD and HIV-associated immunoblastic lymphoma, and those occurring in immunocompetent individuals.

EBV-associated lymphomas in immunocompetent individuals

Burkitt's lymphoma

BL is an aggressive lymphoma associated with EBV infection. It is classified as a non-Hodgkin's lymphoma (NHL) and has the fastest doubling time among human tumors [27]. Based on clinical and epidemiological characteristics BL is subdivided into three categories: endemic BL (eBL), sporadic BL (sBL), and HIV-associated BL. Studies suggest that variations differ in geographical distribution and degree of association with EBV. About 95% of eBL cases are associated with EBV and are commonly found in equatorial Africa and Papua New Guinea [105, 118]. In contrast, only 5–15% of sBL, affecting children and young adults, throughout the world and 40% of HIV-associated BL are EBV positive [115]. Subtypes of BL also differ in clinical manifestation. Typically, eBL presents as tumors affecting the jaw and facial bones, while sBL more commonly arises in the gut and upper respiratory tract, forming tumors in the Waldeyer ring [13, 119]. HIV-associated BL characteristically involves the lymph nodes and bone marrow [12]. For all three types of BL, males are more commonly affected than females [101].

The mechanism by which EBV contributes to the development of Burkitt's lymphoma is not entirely understood. The EBV associated BL demonstrates that the complex interaction of EBV with B cells predisposes to BL development [74, 101]. Malaria infection in endemic regions is considered as another co-factor for the development of BL [16]. It is assumed that hyperstimulation of B cells and suppression of T-cell activity by malaria allow for reactivation of EBV in infected B cells, which consequently increase in numbers. The alternative explanation is that malaria infection compromises EBV-specific immune control, leading to immune escape of an EBV-infected B cell including those in which a c-myc translocation has occurred [11].

In all variations of BL, constitutive activation of the c-myc oncogene through its translocation into one of the immunoglobulin loci is clearly the key factor of the oncogenesis [118]. 80% of all BL shows a t(8:14) translocation; the other observed translocations are t(8:22) and t(8:2) [3, 30]. The translocation is dependent on the enzyme activity of AID (activation-induced cytidine deaminase) [44, 80]. AID is highly expressed in the germinal center (GC) to provide the class switch and hypermutation of the Ig variable region. After translocation, the activated myc can lead to cell growth and proliferation; however, it also leads to apoptosis in the absence of apoptosis-inhibiting signals. These signals may be provided by EBV proteins (EBNA-1) [8, 76]. Some studies have shown BL cases that do not show any MYC translocation, yet still overexpress c-myc. This has been demonstrated for <10% of sBL and linked to miRNA deregulation [1].

Most EBV-positive cases exhibit a restrictive pattern of expression of latent encoded proteins, only expressing EBNA-1 and the EBERs (latency I) [118]. Because EBNA-1 protein is poorly antigenic and has little to no HLA class I response, the CD8+ T-cell response to BL is largely diminished. Various pathways by which BL escapes immune detection by inhibiting both HLA class I- and II-mediated Ag presentation to T cells are essential to the disease pathogenesis [36,72].

It was recently reported that some cases, in addition to EBNA-1 and the EBERs, express EBNA-3A, EBNA-3B, EBNA-3C, and EBNA leader protein but still lack EBNA-2 and the latent membrane proteins [60]. EBNA-1 plays a crucial role in the maintenance and replication of the viral genome, but its oncogenic potential is highly controversial [114,118]. Conversely, as the EBERs are believed to possess anti-apoptotic activity, it has been postulated that they may play an essential role in the oncogenesis of BL [62].

Hodgkin's lymphoma

Hodgkin's lymphoma accounts for about 1% of all cancers and 30% of lymphoid malignancies worldwide [43]. Epidemiologic studies of HL demonstrate a remarkable diversity of the incidence according to age, sex, ethnicity, geographic location and socioeconomic status [21,51]. According to the WHO classification, HL can be histologically divided into four subtypes: lymphocyte predominant (LP), nodular sclerosing (NS), mixed cellularity (MC) and lymphocyte depleted (LD) [38]. Not all subtypes harbor EBV to the same degree. EBV positivity in lymphoma tissue is discerned in 70% of MC Hodgkin's disease, 95% of LD Hodgkin's disease, and 10–40% of NS. LP Hodgkin's disease subtype is almost always EBV negative [24].

The role that EBV plays in HL is still not fully understood. Several lines of evidence including increased risk in individuals with a past history of infectious

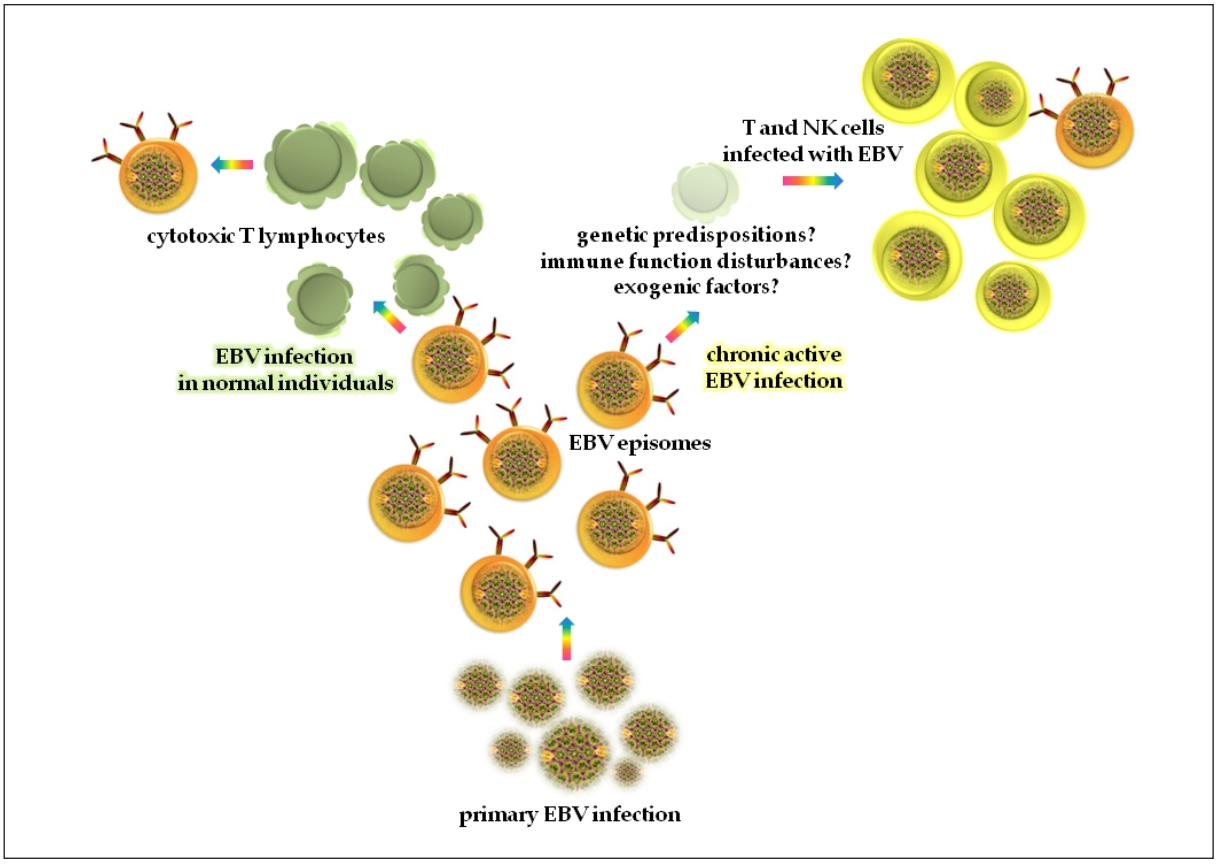

Fig. 2. Pathogenesis of CAEBV

mononucleosis [2], elevated antibody titers to EBV viral capsid antigen [71] and demonstration of the virus in the malignant cells [110] link EBV to HL. HL is characterized by an expansion of Hodgkin and Reed-Sternberg (HRS) cells representing transformed B cells and constituting a minority of the tumor mass [67]. The feature of HRS cells is constant activation of anti-apoptotic transcription factor NF-κB, essential for HRS cell survival [85].

EBV-positive HL has expression of EBNA-1, LMP-1, LMP-2 and the EBERs, indicative of type 2 latency [28]. HRS cells often have destructive immunoglobulin variable (V) gene mutation and therefore lose expression of the B-cell receptor (BCR). Germinal-centre B cells that acquire such mutations are normally eliminated by apoptosis in the germinal centre. The current scenario for HL is that the expression of latent membrane protein 1 (LMP-1) and LMP-2A may prevent apoptosis by mimicking CD40 and BCR signaling, respectively. [57, 65]. Furthermore, to evoke its own survival, HRS cells employ several mechanisms, which are able to suppress a supportive microenvironment of immune and stromal cells and local immune responsiveness [33]. HRS cells have been shown to produce immunosuppressive cytokines such as IL-10, IL-13 and TGF-β [39,45,58,72] as one of the elements of immune escape in Hodgkin's lymphoma.

T-cell lymphomas

In contrast to its role in B-lymphomagenesis, EBV has only incidentally been associated with T-cell lymphomas. Several types of non-B-cell non-Hodgkin's lymphoma are associated with EBV [48, 52]. We will focus on angioimmunoblastic and nasal T/NK cell lymphoma.

Angioimmunoblastic T-cell lymphoma (AITL) is a rare neoplasm but represents the most common subtype of peripheral T-cell lymphomas [50]. Viral genome is detected in up to 100% of AITL lymph nodes [109]. However, EBV can be detected only in B cells [14]. The presence of EBV in only a subpopulation of cells suggests that EBV infection is secondary to malignancy or that the viral genome has been lost from the malignant cell [99]. AITL is characterized by systemic disease, a polymorphous infiltrate primarily involving lymph nodes, proliferation of high endothelial venules and follicular dendritic cells [113]. Clinically it occurs as a widespread lymphadenopathy, extranodal disease, immune-mediated hemolysis, and polyclonal hypergammaglobulinemia, and presents poor prognosis [46].

Nasal-type T/NK-cell lymphoma is a rare tumor, almost always associated with EBV, prevalent in Asia and especially in China [49]. Nasal T/NK lymphoma cells exhibit several unique genotypic and phenotypic features.

These features include an absence of T-cell antigens, the expression of the NK cell marker CD56, and the absence of T-cell receptor gene rearrangement [112]. The nasal region is the most frequent site of involvement but the tumor may also appear at other extranodal sites such as skin, testis, kidney, upper gastrointestinal tract, and the orbit [23, 88].

Some nasal NK/T-cell lymphomas develop from long-lasting EBV infection termed **chronic active EBV infection (CAEBV).** CAEBV is an EBV-associated syndrome characterized by a variety of serious hematological disorders, including malignant lymphoma. EBV was found to infect circulating T and/or NK cells in patients with CAEBV. These EBV-infected cells express EBNA-1, LMP-1, and LMP-2A, a type II form of EBV latency, which is also observed in nasopharyngeal carcinoma (NPC), HL, and peripheral T-cell lymphoma. CAEBV may thus represent a subset of EBV-associated T- and/or NK-cell lymphoproliferative disorders [56]. Most lymphomas associated with CAEBV have been reported to be nodal T-cell [55, 82] but in some cases extranodal T-cell lymphoma was diagnosed in the skin, kidneys, spleen, pancreas, and meninges [6]. Figure 2 presents the pathogenesis of CAEBV.

EBV-associated lymphomas in immunocompromised individuals

Patients with primary immunodeficiencies such as Wiskott-Aldrich syndrome, severe combined immunodeficiency (SCID) or X-linked lymphoproliferative disease are prone to develop EBV-related lymphoproliferative disorders (LPDs). However, EBV-related LPDs are more frequent in patients with secondary immunodeficiencies with AIDS or in organ transplant recipients who receive immunosuppressive therapy [26].

HIV-associated lymphoproliferative disorders

HIV-associated lymphoproliferative disorders represent a heterogeneous group of diseases, arising in the presence of HIV-associated immunodeficiency. According to the WHO classification, HIV-associated lymphomas are categorized into: (a) lymphomas also occurring in immunocompetent patients, including BL, diffuse large B-cell lymphoma (DLBCL) with centroblastic/immunoblastic features, extranodal marginal zone lymphoma of MALT type, peripheral T-cell lymphoma and HL; (b) lymphomas occurring more specifically in HIV-positive patients, including primary effusion lymphoma and plasmablastic lymphoma of the oral cavity; (c) lymphomas also occurring in other immunodeficiency states, including polymorphic B-cell lymphoma (PTLD-like) [84]. The increased risk for lymphoma among HIV-infected individuals appears to be related to multiple factors, including duration and degree of immunosuppression, induction of cytokines leading to B-cell proliferation, and opportunistic infections with oncogenic herpesviruses such as EBV and HHV-8 [64]. The evidence of EBV involvement in development of HIV-related lymphomas is the demonstration of monoclonal virus in the tumors. EBV is present in approximately 60% of HIV-related lymphomas, but the proportion of virus-positive tumors varies depending on histological subtype [26].

BLs make up the largest group of HIV-associated non-Hodgkin lymphomas, comprising 35–50% of these neoplasms [95]. The presence of latent EBV in BL cells has been shown to promote genetic instability [54], suggesting a mechanism by which latent EBV could contribute to genetic alterations required for the development of BL. Other studies have shown that the priming of circulating EBV-specific CD8+ T cells is dependent on CD4+ T cells [81]. In HIV-infected individuals the CD4+ T-cell count is greatly reduced, leading to diminished CD8+ T-cell activity which permits reactivation of EBV-infected B cells [81]. High frequency of EBV association has been shown in HL (80%–100%) tissues from HIV-infected people. Additionally, EBV-encoded LMP-1 is expressed in all HIV-HL cases [86, 89], which shows that HL in HIV-infected persons appears to be an EBV-driven lymphoma [20].

Immunoblastic DLBCL has a high frequency of EBV positivity (80–90%) with frequent expression of LMP-1 and EBNA-2. LMP-1 plays a crucial role in the transformation of B-lymphocytes by EBV into immortalized human primary B cells [29] by activating NF-κβ and other anti-apoptotic factors [66,108].

DLBCL also gives rise to the **primary central nervous system lymphoma** (PCNSL) in AIDS patients [68]. PCNSL is extremely rare in the general population but occurs in 0.5% of patients with AIDS and shows EBV association in 100% of cases [70].

Most cases of **primary effusion lymphomas** (PELs) are dually infected with EBV and Kaposi's sarcoma associated herpesvirus (KSHV) [75]. While PEL is a rare tumor in immunocompetent individuals, it arises with increased incidence rates in HIV-infected patients. The exact role of EBV is unclear but the fact that both viruses are detected together in most cases suggests that EBV may act as a cofactor in the initiating events (because it can immortalize and transform B cells in vitro) whereas HHV-8 may be the driving force for the tumor [92].

Post-transplant lymphoproliferative disease

EBV has also been linked to most post-transplant lymphoproliferative disease (PTLD) cases, with a near 100% association. Type III latency is exhibited by the EBV-positive B cells in PTLD [15]. The wide expression of the latent EBV-encoded proteins suggests an important role that EBV play in the oncogenic process. The mechanism by which EBV is thought to contribute to the pathogenesis of PTLD is similar to its presumed role in HL. As approximately 50% of PTLD cases are derived from GC B cells lacking a functional BCR because of certain crippling mutations, and because these cells manage to escape apoptosis despite lacking antigen affinity, it is believed that EBV aids in rescuing these cells from apoptosis [18, 102].

PTLD is a spectrum of lymphoid hyperproliferative states that may be observed in solid organ and bone marrow transplant recipients [69]. The majority of cases of post-transplant lymphoma (PTL) are EBV-positive [98]. Iatrogenic immunosuppression leading to primary EBV infection or reactivation of latent EBV infection is followed by polyclonal expansion of B cells. These cells are susceptible to molecular aberrations driving malignant growth [63]. Inadequate T-cell control of EBV-infected B lymphocytes is thought to be critical to the development of EBV-positive PTLDs. Decreased anti-EBV nuclear antigen antibody levels have been associated with an increased risk for PTLD [87]. Other predisposing factors include EBV mismatch between donor and recipient, high levels of immune suppression, transplanted organ type and cytomegalovirus infection [69,96].

However, there is no consensus whether any particular immunosuppressive agent is particularly responsible for PTLD. It seems that the risk of PTLD is rather low in patients treated with prednisone and azathioprine while the data on muromonab-CD3 and various forms of anti-thymocyte globulins suggest they probably increase the risk of PTLD. PTLD is commonest in children under 10 years and adults over 60 years, reaching the highest frequency in pediatric small bowel transplant recipients and the lowest in adult liver transplant recipients (Table 1) [79].

Table 1. Frequency of PTLD in patients after different organ transplantations by age [116].

Organ	Adults (%)	Pediatric (%)
Kidney	1.0-2.3	1.2-10.1
Liver	1.0-2.8	4.0-15.0
Heart/lung	2.4-5.8	6.4-19.5
Lung	4.2-10.0	6.4-19.5
Heart	1.0-6.3	6.4-19.5

The cumulative incidence of PTLD in allogeneic hematopoietic stem cell transplantation (HSCT) recipients is 1.0% (range 0.5-1.8%). Major risk factors for the early development of PTLD in allo-HSCT recipients include the use of unrelated or HLA-mismatched related donors, T-cell depletion of donor marrow, and use of anti-thymocyte globulin or monoclonal anti-T-cell antibodies for the prophylaxis and treatment of acute graft-versus-host disease [106].

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