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Authors

Rezk, Sherif A

Weiss, Lawrence M

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Progress in pathology

Epstein-Barr virus–associated lymphoproliferative disorders

Sherif A. Rezk MD, Lawrence M. Weiss MD*

Department of Pathology, City of Hope National Medical Center, Duarte, CA 91010, USA

Summary Epstein-Barr virus (EBV) is a member of the human herpesvirus family that was initially isolated from a cultured Burkitt lymphoma cell line by Epstein et al in 1964. Subsequent studies have proven that it is the causative agent in most cases of infectious mononucleosis. Primary infection is usually asymptomatic in childhood; but in adulthood, it is associated with a self-limiting infectious mononucleosis syndrome in approximately one third of the cases. EBV has been linked to many human neoplasms including hematopoietic, epithelial, and mesenchymal tumors. In this review, we will only discuss the EBV-associated lymphoproliferative disorders, dividing them into B-cell, T/NK-cell, and HIV-related lymphoproliferative disorders.
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1. Introduction

Epstein-Barr virus (EBV), a member of the human herpesvirus family, is a linear, double-stranded DNA virus that was initially isolated from a cultured Burkitt lymphoma cell line by Epstein et al in 1964 [1]. Subsequent studies have proven that it is the causative agent in most cases of infectious mononucleosis [2]. Currently, it is estimated that more than 90% of the adult population worldwide are infected by the virus [3]. Primary infection is usually asymptomatic in childhood; but in adolescence or adulthood, it is associated with a self-limiting infectious mononucleosis syndrome in approximately one third of the cases [4,5]. The virus is secreted in the saliva, and human infection occurs through oral transmission [6]. Oropharyngeal infection results in a lytic (productive) infection followed by infection of circulating B cells, leading to persistence of the viral DNA

as an episome in the nucleus, thus establishing latent infection [7,8].

In lytic infection, EBV-encoded genes selectively replicate virion components including viral DNA genomes and proteins. In latent infection, EBV-encoded genes, which include 6 nuclear antigens (EBNA 1, 2, 3A, 3B, 3C, and LP), 3 latent membrane proteins (LMP 1, 2A, and 2B), 2 small noncoding RNAs (EBER1 and EBER2), and *Bam*HI-A rightward transcripts, maintain the existence of the viral genome and enable it to evade immune surveillance [3,9]. A summary of the most important latent proteins is tabulated in Table 1. Three distinct latency programs that are equivalent to the differentiation state of B cells have been postulated after analysis of EBV-infected B cells in cell lines and seropositive individuals [3,10]. The presence of different EBV latency programs is thought to have evolved in order for EBV-infected cells to survive in the face of an adaptive immune response and surveillance [10,11].

Type III latency (growth program) pertains to EBV-infected naive B cells that express all the latent antigens (Fig. 1). The naive infected B cells enter the germinal center

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* Corresponding author.
E-mail address: lweiss@coh.org (L. M. Weiss).
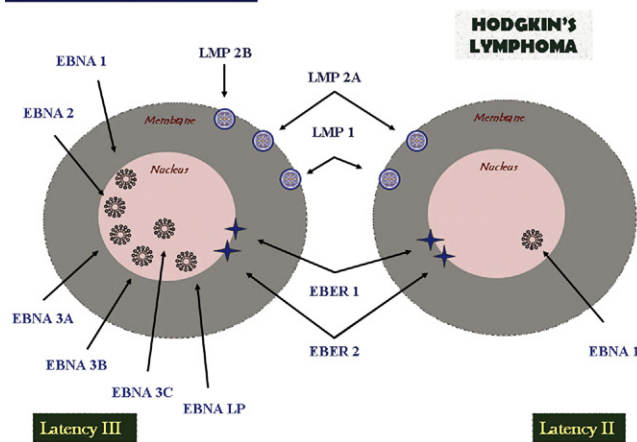
Table 1 Latent EBV-encoded genes

EBV-encoded genes	Location	Function	Latency type
EBNA-1	Nucleus	Considered the viral genome maintenance protein, where it binds to the origin of replication of the EBV episome leading to replication of the virus DNA [8]. It also plays a role in the transcriptional regulation of other latent nuclear and membranous proteins. It is not recognized by cytotoxic T cells.	I, II, III
EBNA-2	Nucleus	Transcriptional regulator and activator of several cellular and viral genes, such as LMP-1 and LMP-2 [8]. It has also been reported that it may target the c-*MYC* oncogene, thus affecting EBV-induced B-cell proliferation [69].	III
EBNA-3	Nucleus	Transcriptional regulator that influences viral and cellular gene expression in EBV-infected cells and may play a role in alteration of the B-cell homing process [10]. It may also play a role in B-cell transformation.	III
LMP-1	Membrane	Considered the main transforming protein of EBV and the major effector of virus-induced cellular changes. It inhibits apoptosis by activating the NF-κB pathways leading to upregulated expression of bcl-2 and other target genes. It can also mimic CD40-induced signaling pathway.	II, III
LMP-2	Membrane	An intrinsic membrane protein that prevents EBV-infected cells from entry into the lytic cycle by sequestering tyrosine kinases from BCR, resulting in inhibition of BCR signaling. It also can mimic BCR and replace survival signals for B cells, normally supplied by BCR.	II, III
EBER1 and EBER2	Nucleus	Nonpolyadenylated RNAs that are not essential for the EBV-induced transformation of B lymphocytes. They are mainly used for the clinical detection of the virus because of their abundant expression. They can induce production of IL-10, which might suppress cytotoxic T cells and stimulate growth of infected B cells. EBERs have also been thought to play a role in modulation of pathways important in interferon response.	I, II, III

(GC) where they proliferate and clonally expand, thus increasing the EBV-infected pool of cells. These GC infected cells show a restricted EBV gene expression pattern (EBNA-1, LMP-1, LMP-2), which is referred to as the *type II latency* (default program) [10]. The infected GC cells then differentiate into memory B cells, which function as the long-term reservoir for EBV. Most of the infected memory B cells in the periphery seem not to express any of the viral antigens (considered by some as type 0 latency); but some only express EBNA-1, which has been referred to as *type I*

latency [12,13]. The EBV latency patterns in different EBV-associated diseases are summarized in Table 2.

EBV has been linked to many human neoplasms including hematopoietic, epithelial, and mesenchymal tumors. It has been associated with almost all cases of nasopharyngeal carcinoma [14], a subset of gastric carcinomas [15], lymphoepitheliomas of a variety of foregut sites [14], inflammatory pseudotumors of the liver and spleen [16], and HIV-associated smooth muscle neoplasms [17]. In this review, we will only discuss the EBV-associated lymphoproliferative disorders, dividing them into B-cell, T/NK-cell, and HIV-related lymphoproliferative disorders.

1.1. EBV-associated B-cell lymphoproliferative disorders

Despite its documented infection of T lymphocytes and epithelial cells in certain circumstances, EBV has a major predilection for B cells because they act as the reservoir for it to persist [4]. Consequently, the persistence of latent EBV genes in B cells results in a carrier state; and in certain occasions, transformation into malignant B-cell lymphomas may occur. Because of the preferential infection of B cells, B-cell lymphomas predominate among the EBV-related lymphoproliferative disorders.

EBV-associated B-cell lymphoproliferative disorders include Hodgkin lymphoma, Burkitt lymphoma, posttransplant

Fig. 1 The different EBV latent encoded proteins expressed in type III latency program and in Hodgkin lymphoma (type II latency).

Table 2   EBV latency patterns in different lymphoproliferative disorders

Disease	EBV latency programs
EBV-associated B-cell lymphoproliferative disorders	
Hodgkin lymphoma	Type II
Burkitt lymphoma	Type I
PTLD	Type III/type II
Lymphomatoid granulomatosis	Type III
Pyothorax-associated lymphoma	Type III
Senile EBV-associated B-cell lymphoproliferative disorders	Type III/type II
EBV-associated T/NK-cell lymphoproliferative disorders	
AILT	Presumed type II
Extranodal nasal T/NK-cell lymphoma	Type II
Hepatosplenic T-cell lymphoma	Not known
Nonhepatosplenic γδ T-cell lymphomas	Type II
Enteropathy-type T-cell lymphoma	Presumed type II
Peripheral T-cell lymphoma	Type II
EBV-associated HIV-related lymphoproliferative disorders	
Primary CNS lymphoma	Type III
Primary effusion lymphoma	Type II
Plasmablastic lymphoma	Type 0 (only EBERs expressed)

lymphoproliferative disorders (PTLDs), lymphomatoid granulomatosis, pyothorax-associated lymphoma, and senile EBV-associated B-cell lymphoproliferative disorders. Hodgkin lymphoma will be discussed among the B-cell disorders because it has a B-cell origin and the role of EBV in the pathogenesis of the disease is probably mediated through infected B cells. Although primary effusion lymphoma and plasmablastic lymphoma are B-cell lymphomas, they will be discussed under HIV-related disorders. Furthermore, angioimmunoblastic T-cell lymphoma (AILT) will be discussed under T-cell disorders despite the fact the EBV acts predominantly through infecting B cells and not T cells.

Hodgkin lymphoma is a distinct disorder in which the characteristic neoplastic cells, known as *Reed-Sternberg cells* (HRS), are interspersed among an inflammatory milieu and only constitute about 2% of total tumor mass. Since it was initially described in 1832 by Sir Thomas Hodgkin [18], many classifications have been postulated for the disease. The most recent World Health Organization (WHO) classification divides Hodgkin lymphoma into classic and nonclassic entities based on different morphological, phenotypic, and molecular features [19]. Nodular lymphocyte–predominant Hodgkin lymphoma represents the nonclassic entity, whereas classic Hodgkin lymphomas include the

nodular-sclerosis, mixed-cellularity, lymphocyte-rich, and lymphocyte-depleted subtypes [19]. Fueled by the indeterminate immunophenotype possessed by HRS cells, the origin of HRS cells was up for intense debate for many years. The scarcity of HRS cells within the tumor tissue was a limiting factor for many studies in the past to accurately apply many standard molecular techniques. However, after isolation of single HRS cells and analyzing them using a single-cell polymerase chain reaction (PCR), it was determined that they are derived from GC B cells as a result of crippling mutations [20,21]. A rare T-cell origin has also been postulated in about 2% of the cases [22].

The identification of elevated antibodies titers to EBV antigens in Hodgkin lymphoma patients reported by Levine et al [23] in the early 1970s prompted other scholars to further study and investigate a potential role that EBV may play in the pathogenesis of Hodgkin lymphomas. In 1987, EBV DNA was initially detected by Weiss et al in Hodgkin lymphoma specimens using Southern blot hybridization studies [24]; however, localizing EBV DNA to HRS cells was not determined until a couple of years later by using in situ hybridization technique [25]. Subsequently, single-cell PCR has also confirmed the presence of EBV DNA in individual HRS cells [26].

EBV is more commonly associated with classic Hodgkin lymphoma, especially the mixed-cellularity subtype [9]. The nonclassic nodular lymphocyte–predominant Hodgkin lymphoma cases are very rarely associated with EBV [27]. Underdeveloped countries have an increased incidence of EBV-positive cases, which may be attributed to the existence of an underlying immunosuppression [12,28]. This is supported by the higher EBV-positive rates in HIV-positive Hodgkin lymphoma patients [29]. Sex and ethnicity are also factors in the epidemiology of EBV-positive Hodgkin cases, where males from a Hispanic or Asian (Chinese) origin tend to be more commonly affected [12,30]. A bimodal age distribution has been recognized for EBV-positive Hodgkin lymphoma patients; children and the older-age group tend to have much higher rates than young adults, the explanation of which may rely on the more competent immune surveillance in young adults as compared with the less developed or declined immune system in children and older individuals, respectively [30].

To better comprehend the role of EBV in the pathogenesis of Hodgkin lymphoma, one must understand the normal differentiation process of B cells within the GC (Fig. 2). Upon encountering an antigen, naive B cells become activated and migrate into the dormant B-cell follicles (primary follicles), undergo blast transformation, and differentiate into centroblasts (large noncleaved cells). The proliferating centroblasts activate the process of somatic hypermutations within the immunoglobulin variable (V) region, which results in marked intraclonal diversity [31]. Centroblasts then differentiate into centrocytes (small cleaved cells), which are positively selected based on the affinity of their B-cell receptor (BCR) to process the antigen
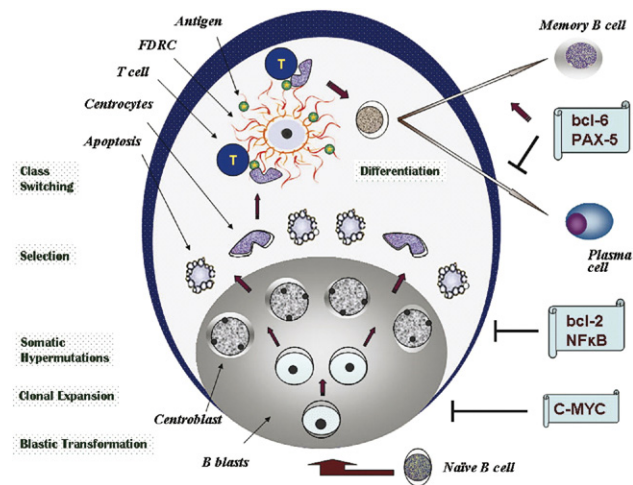
Fig. 2 The projected scheme of B-cell differentiation and GC formation. Naive B cells are first activated in the paracortical area, undergo blastic transformation, rapidly duplicate, and clonally expand within hours, giving rise to centroblasts. Numerous somatic hypermutations occur within the immunoglobulin V region, resulting in marked intraclonal diversity to increase the affinity for the antigen trapped within the follicular dendritic meshwork. Centroblasts then differentiate into the less proliferative centrocytes, which are positively selected based on the affinity of their BCR to process the antigen. Centrocytes with mutations that decrease their affinity for the antigen are negatively selected and undergo programmed cell death (apoptosis). After an additional heavy chain class switching, the positively selected B cells leave the GC and differentiate into either memory B cells or plasma cells.

trapped within the follicular dendritic reticular cell (FDRC) meshwork. Centrocytes with mutations that lessen their affinity for the antigen are negatively selected and undergo programmed cell death (apoptosis). After an additional heavy chain class switching, the positively selected B cells leave the GC and differentiate into either memory B cells or plasma cells [31].

In classic Hodgkin lymphoma cases, molecular analysis has shown that the rearranged V regions of HRS cells contain somatic mutations but lack the intraclonal diversity, with considerable amount of such cases carrying nonsense or crippling mutations [21]. Under normal circumstances, such cells are usually eliminated by apoptosis in the GC unless they are rescued by receiving survival signals such as activation of BCR and CD40 receptors. However, in Hodgkin cases, these cells survive, indicating that HRS cells are derived from preapoptotic GC B cells that, aided by certain transforming events, have escaped the programmed cell death process. Some investigators speculate that the near-total loss of the B-cell identity in HRS cells may have enabled them to escape the selection process in the GC [32].

The pattern of expression of latent EBV-encoded genes in HRS indicates an important role for EBV in the rescue of these preapoptotic cells [8]. HRS cells exhibit type II latency, which includes LMP1, LMP2, EBNA1, and the EBERs (Fig. 1) [9]. LMP1 and LMP2A may mimic and replace

survival signals induced by activated CD40 and BCR, respectively. LMP1 resembles a constitutively active CD40 receptor [33], whereas LMP2A has been reported to mimic the presence of BCR in transgenic mice [34]. In addition to mimicking an activated CD40 receptor, LMP1 has also been postulated to prohibit apoptosis by upregulating the antiapoptotic protein bcl-2 [35] and mediating the activation of the nuclear factor–κB (NF-κB) signaling pathway [36]. Aside from inhibiting apoptosis, the activated NF-κB pathway plays a crucial role in the induction of proliferation in HRS cells [36]. NF-κB transcription factors are kept inactive by interactions with the inhibitor IκB. Signaling through various cell-surface receptors activates IκB kinases, which phosphorylate IκB, thus promoting its degradation and the eventual activation of the NF-κB pathway [31]. Although some have postulated a potential role of LMP1 in the deregulation of IκB proteins [37], the exact mechanism of activation of the NF-κB pathway by LMP1 remains largely unknown.

Another potential role for LMP1 is the downregulation of CD99. Loss of CD99 has been reported to be associated with generation of B cells with classic Hodgkin immunophenotype [38]. Kim et al have reported that LMP-1 transcriptionally reduces the expression of CD99 in Hodgkin lymphoma cases, but the mechanism of which is unknown [39]. LMP2 plays an important role in maintaining the EBV latency status and preventing the transition into the lytic cycle. However, other than its postulated role in rescuing HRS cells by mimicking the presence of BCR, its exact function in the pathogenesis of Hodgkin lymphoma remains to be determined. To our knowledge, EBNA1 has not been linked yet to any oncogenic activity in human beings.

Burkitt lymphoma was first described in children in equatorial Africa by Denis Burkitt in 1958 [40]. It is a highly proliferative B-cell tumor that includes 3 variants: endemic (affecting children in equatorial Africa and New Guinea), sporadic (children and young adults throughout the world), and immunodeficiency related (primarily in association with HIV infection) [41]. EBV has been detected in virtually all cases of the endemic variant, 15% to 20% of the sporadic variant, and 30% to 40% of the immunodeficiency-related variant [42]. The variable EBV association in the 3 variants has prompted many to contemplate the possibility of the virus being a passenger in the neoplastic process and not the initiating factor. In all variants, irrespective of the EBV status, constitutive activation of the c-*myc* oncogene through its translocation into one of the immunoglobulin loci is clearly the key factor in the oncogenesis of Burkitt lymphoma [41,42]. The detection of somatic hypermutations in the V region of the immunoglobulin genes and the phenotype of the Burkitt lymphoma cells indicate a GC cell origin of the lymphoma [8].

Most EBV-positive cases exhibit a highly restrictive pattern of expression of latent encoded proteins, only expressing EBNA1 and the EBERs (latency I) [42]. However, it has been recently reported that some cases,

in addition to the EBNA1 and the EBERs, express EBNAs 3A, 3B, 3C, and LP but still lack EBNA2 and the latent membrane proteins [43]. That restrictive latency pattern has prompted an intense ongoing debate about the role of EBV in the pathogenesis of Burkitt lymphoma. EBNA1 plays a crucial role in the maintenance and replication of the viral genome, but its oncogenic potential is highly controversial [42,44]. As the EBERs are believed to possess antiapoptotic activities, as well as the ability to induce the expression of interleukin (IL)-10, which may promote cell growth and survival, it has been postulated that they may play an essential role in the oncogenesis of Burkitt lymphoma [45,46]. This postulation, although endorsed by many investigators, is still debatable; and to date, the role of EBV in the pathogenesis of Burkitt lymphoma remains hypothetical.

Another controversial issue is the possibility of Burkitt lymphoma being a tumor of latently infected memory B cells rather than being of a GC cell origin. This theory is based upon the highly restricted pattern of the EBV-latent proteins, similar to that seen in memory B cells in healthy carriers [13]. However, this theory is heavily negated by the phenotype of the Burkitt lymphoma cells, which is more consistent with a GC origin. Moreover, analysis of the chromosome breakpoints in the MYC translocation indicates that these translocations have occurred because of either somatic mutation or class switch recombination, which are both unique processes for the GC [47].

PTLD is a clinicopathological entity encompassing a heterogeneous group of disorders that follow solid organ transplant or bone marrow allograft as a consequence of immunosuppression and range from reactive hyperplasia to malignant monoclonal forms [48,49]. According to the WHO classification, they are divided into early lesions (reactive plasmacytic hyperplasia and mononucleosis-like syndrome), polymorphic lesions, monomorphic lesions, and Hodgkin-like lesions [48]. A GC or a post-GC origin has been recognized for PTLD because of the detection of somatic mutations in a considerable percentage of cases [13].

The risk of developing PTLD varies considerably, which is mainly dependent on several factors such as the transplant type, the age of the patient, the immunosuppressant regimen, and the EBV status. EBV has been linked to most PTLDs, with a near 100% association in the early-occurring cases (within a year) and in PTLD-associated Hodgkin lymphoma [50]. The EBV-negative PTLDs constitute approximately 20% of all cases, have a tendency to late occurrence (>5 years post transplant), and have an unknown etiology [48]. Type III latency is exhibited by the EBV-positive B cells in PTLD, although some studies have reported a more restricted latency pattern [51]. The wide expression of the latent EBV-encoded proteins strongly suggests an important role that EBV may play in the oncogenic process. This is also supported by several other factors including the near 100% EBV association with PTLD cases (especially early-occur-ring cases), the numerous EBV-positive cells detected by in situ hybridization, and the high EBV viral load measured by PCR in the peripheral blood that declines after decreasing the immunosuppression dosage [48].

The mechanism by which EBV is thought to contribute to the pathogenesis of PTLD is similar to its presumed role in Hodgkin lymphoma. Because 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 an imminent programmed cell death [52,53]. As in Hodgkin cases, LMP1 and LMP2A may replace survival signals induced by activated BCR and CD40 receptors and also activate the NF-κB signaling pathway, inducing proliferation of neoplastic cells.

The decreased cytotoxic T-cell surveillance because of immunosuppression in PTLD patients is also believed to greatly facilitate the actions of EBV. The similar role that EBV is thought to play in inducing the survival and neoplastic transformation of infected GC cells in both PTLD and Hodgkin lymphoma, in addition to the near 100% EBV positivity in PTLD-associated Hodgkin lymphoma, has led some investigators to speculate a connection between the 2 diseases and the possibility that EBV infection and its GC effects may be the initiating role in the pathogenesis of both entities [52].

Lymphomatoid granulomatosis is a rare angiocentric and angiodestructive B-cell lymphoproliferative disorder that is composed predominantly of reactive T cells and fewer neoplastic EBV-positive B cells [54]. The most common site of involvement is the lung, with less frequent involvement of other extranodal sites such as the skin, kidney, liver, and central nervous system (CNS) [55]. Since it was first described in 1972 by Liebow et al [56] and for nearly 2 decades, lymphomatoid granulomatosis was thought to be a T-cell lymphoproliferative disorder because of the predomi-nance of CD4-positive helper T cells and the failure to detect any associated B-cell gene rearrangements [57,58].

The failure to detect B-cell gene rearrangements at that time could be explained by the use of less sensitive techniques and also the scarcity of neoplastic B cells within the tumor (similar to Hodgkin cases). The detection of EBV that was confined to B cells led to the hypothesis that lymphomatoid granulomatosis may represent a B-cell disorder [59]. That hypothesis was later confirmed by the ability to detect immunoglobulin heavy chain gene rearrangements in EBV-infected B cells [60,61]. A 3-tier grading system has been proposed for lymphomatoid granulomatosis that relates to the number of EBV-positive B cells within each case (grade I: <5, grade II: 5-20, and grade III >20 cells) [54].

The latency pattern for EBV has not been extensively studied in lymphomatoid granulomatosis; but one group has reported the detection of LMP1 and EBNA2 by immuno-histochemistry and the EBERs by in situ hybridization, which is indicative for type III latency [62]. The near 100%

EBV association with lymphomatoid granulomatosis and the presumed wide expression of EBV latent encoded proteins strongly infer that EBV is not just an innocent bystander but may play a crucial role in the pathogenesis of the disease. The presence of lymphomatoid granulomatosis in a considerable amount of immunosuppressed patients and the presumed latency III pattern of expression make us hypothesize that the role of EBV in the pathogenesis of lymphomatoid granulomatosis is similar to that seen in PTLD, where EBV is believed to play a role in the transformation of infected B cells in the absence of adequate T-cell surveillance [63].

Pyothorax-associated lymphoma is an entity that was first described in Japanese patients by Iuchi et al in 1987 [64] and was later incorporated into the WHO classification of lung and pleural tumors in 2004 [65]. Pyothorax-associated lymphoma is considered to be a subcategory of diffuse large B-cell lymphoma that typically exhibits immunoblastic morphology, tends to present as a pleural mass, and results from long-standing pyothorax from pulmonary tuberculosis [65,66]. Its reported association with EBV has ranged from 70% to 100% of the cases [65]. Type III latency has been proposed because the EBV latent encoded proteins LMP1, EBNA1, EBNA2, and EBERs are expressed [66]. The exact role of EBV in the oncogenesis of pyothorax-associated lymphoma has yet to be determined, although some studies have suggested that the production of IL-6 and IL-10 by EBV, in addition to the ability of EBNA1- and LMP1-expressing B cells to escape immunosurveillance in immunocompromised patients, may provide some clues for a potential role for EBV [66-68].

Senile EBV-associated B-cell lymphoproliferative disorders constitute a provisional entity, recently described by Oyama et al, in which elderly (>60 years old) immunocompetent patients develop EBV-associated B-cell lymphomas with a predilection for involvement of extranodal sites [69]. The entity was further subdivided into a polymorphic category (broad range of B-cell differentiation in an inflammatory background) and a large cell category (monomorphic large cells) [69]. EBV was detected in all cases; and a latency III program was most often expressed, although some cases lacked EBNA2 expression (latency II) [69,70]. The variable presence of EBNA2 expression may be attributed to the variable degrees of immune surveillance in aging individuals.

1.2. EBV and T/NK-cell lymphoproliferative disorders

Most EBV-related lymphoid malignancies are of a B-cell origin [42]. However, since the EBV association with T-cell proliferation was first described [71], many other T-cell lymphoproliferative entities have been linked to EBV, especially in Asia and Latin America. EBV can infect CD4+ and CD8+ peripheral blood T cells as well as NK cells

in a minority of patients with infectious mononucleosis [72]. However, most EBV-associated T-cell lymphomas exhibit a cytotoxic phenotype (granzyme B and TIA-1 positive), which suggests that these tumors may have resulted somehow from the proliferating cytotoxic T cells trying to kill the EBV-infected cells [73]. Because T cells are refractory to EBV infection in vitro (in contrast to B cells), the exact mechanism of how EBV accesses or infects the T cells is largely unknown [42].

Most EBV-associated T-cell lymphomas arise after chronic active EBV infection; and usually, EBV detection indicates an aggressive process or confers a worse prognosis [42]. Patients usually exhibit prolonged fever, hepatosplenomegaly, multiple sites of lymphadenopathy, weight loss, and multiorgan failure, with a median survival of only a few months despite intensive chemotherapy [72]. The immune status of patients usually does not affect longevity, where d'Amore et al have reported a poor prognosis in immunocompetent patients with EBV-associated T-cell lymphomas based on studying a register-based population [74]. In most T-cell lymphoproliferative disorders, a type II latency is recognized in which the expressed EBV latent encoded proteins are LMP1, 2A, and 2B; EBNA1; and EBERs [42,75].

The exact role of EBV in the oncogenesis of T-cell lymphomas is still hypothetical, although Yang et al have reported that increased IL-9 levels induced by the EBERs possess antiapoptotic effects and promote T-cell proliferation and transformation [75]. Another theory regarding EBV and T-cell oncogenesis is similar to Hodgkin lymphoma pathogenesis, in which it has been documented that LMP1 may mimic or act as a viral analogue for members of the family of tumor necrosis factor (TNF) receptors, thereby transmitting growth signals through cytoplasmic TNF receptor–associated factors [76]. Members of the TNF family include CD40, which was previously discussed in the section on Hodgkin lymphoma. Because TNF-α levels, which may be the cause of fever and weight loss in T-cell lymphomas, are believed to reliably correlate with disease activity and with EBV infection, a few authors have suggested that monitoring TNF-α levels would be a useful prognostic marker in EBV-associated peripheral T-cell lymphoma and that agents against TNF-α may be a therapeutic option [77].

T-cell lymphoproliferative disorders that have been reported to be EBV associated include a subset of peripheral T-cell lymphomas [78,79], AILT [80,81], extranodal nasal type NK/T-cell lymphoma [82], enteropathy-type T-cell lymphoma [83,84], γδ T-cell lymphomas (hepatosplenic and nonhepatosplenic) [85,86], T-cell lymphoproliferative disorders after chronic EBV infection [87], EBV-associated cutaneous T-cell lymphoproliferative disorders (especially in Asia) [88], and aggressive NK-cell leukemia/lymphoma [89].

AILT is a systemic lymphoproliferative disorder that mainly affects older individuals and is characterized by a

polymorphous lymphoid infiltrate; florid vascular proliferation; FDRC proliferation; regressed or, more uncommonly, hyperplastic GCs; and constitutional symptoms (generalized lymphadenopathy, fever, skin rash, hepatosplenomegaly, and polyclonal hypergammaglobulinemia). Clonal rearrangements of the T-cell receptor genes have been detected in most cases [90]. EBV was first detected in AILT cases using Southern blot [80] and subsequently by PCR [81,91] in a variable number of B cells, which raised the question of a potential role for EBV in the pathogenesis of the disease, although T cells are generally not EBV infected. EBV-driven B-cell lymphomas can also superimpose or complicate the course of AILT on a few occasions in which the AILT-associated immunodeficiency followed by the immunosuppressive effects of chemotherapy may have created an ideal environment for a variable number of EBV-infected B cells to proliferate and transform [92].

The EBV-positive B cells have been determined to have ongoing somatic hypermutation, a hallmark of GC cells; however, these mutations are nonfunctional [93]. These crippling mutations are almost restricted to the EBV-infected cells and not detected in EBV-negative cells, which assumes a potential influence of EBV on these proliferating cells [93]. Although crippling mutations are also seen in classic Hodgkin lymphoma, HRS cells lack the intraclonal diversity because of the shutdown of the ongoing somatic mutations, in contrast to the EBV-infected B cells in AILT that continue to undergo somatic mutations even with the presence of crippling mutations [94]. The reasons for the sustained somatic hypermutation status are largely unknown, although it has been speculated by some that the rich FDRC meshwork and the increased number of CD4-positive helper T cells in AILT cases may stimulate the proliferating B cells to undergo somatic mutations and probably escape apoptosis [8].

The latency pattern for EBV is not known as well, although some have assumed a restricted latency II program similar to that seen in other EBV-associated T-cell lymphoproliferative disorders [93]. This postulation can also be supported by the fact that most of the subsequent EBV-associated B-cell proliferations that follow AILT in few occasions express LMP1 and the EBERs, which is consistent with type II latency [92].

Extranodal nasal NK/T-cell lymphoma, previously known as *polymorphic reticulosis*, is an angiocentric and angiodestructive tumor associated with prominent necrosis, which predominantly involves the nasal cavity and has a geographical predilection for Asia and Central America [95]. The EBV association has evolved since the viral genomes were detected in Asian patients by Southern blot and in situ hybridization techniques [96-98]. A latency II program has been reported, which includes the expression of the latent EBV proteins LMP1, EBNA1, and EBER [99]. As in all EBV-associated T-cell lymphoproliferative disorders, the exact mechanism by which EBV gains access and infects T cells has yet to be determined.

Similar to normal NK cells and in contrast to infected B cells, EBV-infected NK cells have been found to require IL-2 for growth and proliferation even with the expression of LMP1 and other type II latency proteins [100,101]. Moreover, the reduction in LMP1 levels in treated cell lines does not lead to growth inhibition or apoptosis within the cells [102]. This, in theory, argues against EBV involvement in the process of transformation and proliferation of the neoplastic T cells [100,101]. One study has suggested, however, that LMP1 may increase the sensitivity of the infected cell to the growth-promoting effects of IL-2 [101].

Hepatosplenic T-cell lymphoma is a rare aggressive subtype of peripheral T-cell lymphoma derived from cytotoxic T cells, usually of the $\gamma\delta$ T-cell receptor type, and is characterized by hepatosplenomegaly and cytopenias [85,103]. Because $\gamma\delta$ T cells have preferential homing to the sinusoidal areas, marked sinusoidal infiltration is noted in both the liver and spleen [104]. EBV has been reported to be not associated with hepatosplenic T-cell lymphoma in most studies [103,105,106]; however, few studies have reported the detection of EBV genome by Southern blot and in situ hybridization in patients with the disease [85,107]. A hypothesized possible role for EBV in the pathogenesis of the disease can be debated because of the inconsistent EBV detection, although one may argue that it may play a role via chronic antigen exposure [85].

Nonhepatosplenic $\gamma\delta$ T-cell lymphomas, like the hepatosplenic entity, are rare disorders with a predilection for sinusoidal infiltration. They can occur in the skin, intestine, nose, lymph nodes, and other extremely rare sites such as the lung and thyroid [86,107]. In contrast to the hepatosplenic form, the nonhepatosplenic forms have been more consistently reported to be associated with EBV [86,108]. The EBERs have been detected by in situ hybridization on a consistent basis; and LMP1 (but not EBNA2) has been detected by immunohistochemistry in a few studies, which indicates a restricted pattern of latent EBV expression (type II latency) [86,108].

Enteropathy-type T-cell lymphoma is an aggressive tumor of intraepithelial T lymphocytes that is common in areas with a high prevalence of celiac disease [109]. The association with EBV is not clear, although a few studies have reported detection of EBV by PCR and in situ hybridization, and rare LMP1 expression by immunohistochemistry [83]. One study has compared EBV association based on geographical and ethnic guidelines, where EBV was detected consistently by PCR and in situ hybridization in patients from Mexico and Central America, whereas rare EBV expression was noted in patients from Western Europe [84].

1.3. EBV And HIV-related lymphoproliferative disorders

The incidence of lymphoproliferative disorders is greatly increased in HIV-positive individuals, with lymphoma ranking second (after Kaposi sarcoma) as the most frequent

malignancy encountered in patients with AIDS [12]. Since the introduction of the highly active antiretroviral therapy, the incidence of lymphoma in AIDS patients has decreased significantly [110]. Most HIV-associated lymphoproliferative disorders are highly aggressive and of a B-cell origin [111,112]. Hodgkin lymphoma is reported to have an 8-fold increased incidence in HIV-positive individuals [113].

HIV-related lymphomas are a heterogeneous group of diseases that include (1) lymphomas that can occur in immunocompetent individuals (HIV negative) such as Burkitt lymphoma and diffuse large B-cell lymphoma (often involving the CNS) and (2) lymphomas that occur almost exclusively in the setting of HIV infection such as primary effusion lymphoma and plasmablastic lymphoma of the oral cavity [114]. Several factors are thought to play a role in the pathogenesis of these lymphomas, including genetic abnormalities, chronic antigen stimulation, cytokine deregulation, and possible roles for human herpesvirus 8 (HHV-8) and EBV [115]. EBV has been reported to be detected in up to 60% of all HIV-related lymphomas, including nearly 100% of primary CNS lymphomas, 80% of diffuse large B-cell lymphoma with immunoblastic features, 30% to 50% of Burkitt lymphomas, 60% of plasmablastic lymphomas, 70% of primary effusion lymphoma, and nearly 100% of Hodgkin lymphomas arising in the setting of HIV [115-117].

Because of the heterogeneity of the HIV-related disorders, different patterns of latent EBV gene expression have been described. In the first subgroup of disorders that can occur in immunocompetent individuals, the pattern of EBV expression coincides, more or less, with the histologic subtype of lymphoma irrespective of the HIV status. In the second group of disorders (HIV near-specific lymphomas), the EBV expression is described below. As in most EBV-associated lymphoproliferative disorders, the role of EBV in the pathogenesis of the HIV-related lymphoproliferative disorders is speculative at the current time. In diffuse large B-cell lymphoma with immunoblastic features, some researchers strongly believe that the high EBV association with these tumors (80%) and the consistent expression of LMP1 indicate an EBV-driven proliferation [118,119].

Primary CNS lymphomas constitute approximately 20% to 25% of all HIV-related lymphomas and have a thousandfold increased incidence in AIDS patients, although the incidence has decreased significantly since the introduction of highly active antiretroviral therapy [111,115,120]. These tumors have a tendency to occur late in the course of HIV infection and show EBV association in virtually 100% of the cases [121]. A few studies have reported that detection of EBV in the cerebrospinal fluid of HIV-positive patients with a CNS lesion infers a diagnosis of lymphoma [122,123]. These lymphomas have been reported to express all EBV latent encoded proteins (latency III), although the role of EBV in the pathogenesis of these disorders remains unknown [121].

Primary effusion lymphoma is a rare and distinct tumor that affects body cavities without a detectable tumor mass [124]. The neoplastic cells have an indeterminate phenotype, where they are CD45 and CD138 positive but negative for pan B-cell markers; however, at the molecular level, unequivocal immunoglobulin gene rearrangements and somatic hypermutations indicate a post-GC B-cell origin [125,126]. Primary effusion lymphoma is predominantly associated with HHV-8 and has been reported to have a variable association with EBV [126]. The consistent detection of both viruses in up to 70% of the cases suggests a possible role for the 2 viruses in the tumorigenesis of the disease [116]. The expression of EBV latent encoded proteins is restricted to EBNA1, LMP1, LMP2A, and EBERs, which is consistent with type II latency [127]. Again, the exact role of EBV has been debated; but the fact that both viruses are detected together in most of the cases suggests that EBV may act as a cofactor in the initiating events (because it can immortalize and transform B cells in vitro and HHV-8 cannot), whereas HHV-8 may be the driving force for the tumor [126].

Plasmablastic lymphoma is a rare, aggressive entity mostly reported in the oral cavity in HIV-positive patients that has been recently recognized as a subtype of diffuse large B-cell lymphoma [128,129]. Occurrence outside the oral cavity and in HIV-negative patients has been rarely reported [130]. EBV has been detected in these patients in about 60% of the cases regardless of the HIV status [117,128]. In contrast to other B-cell lymphoproliferative disorders, EBV expression is restricted to the EBERs, which correlates with previous work showing a marked reduction in the expression of EBV latent proteins with terminal B-cell differentiation into plasma cells [131,132]. A potential role for EBV in the pathogenesis of the disease remains unknown, especially with the highly restricted latency expression pattern.

In summary, EBV infects most of the world's adult population, resulting in acute symptoms in a minority of patients; but it is the persistence of EBV in the human body as a latent infection that has been the subject of numerous studies because of its association with neoplastic transformation. Lymphoproliferative disorders constitute most of the EBV-associated neoplasms, in which the mechanism of the induced transformation is better understood in some disorders than in others. Further studies to provide better understanding of the pathophysiology of EBV-induced or EBV-associated transformation may lead to the development of novel therapies for the virus-associated disorder.

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