Journal of Pathology
J Pathol 2015; 235: 312–322
Published online in Wiley Online Library
(wileyonlinelibrary.com) DOI: 10.1002/path.4459

INVITED REVIEW

The Epstein–Barr virus and the pathogenesis of lymphoma

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Abstract

Since the discovery in 1964 of the Epstein–Barr virus (EBV) in African Burkitt lymphoma, this virus has been associated with a remarkably diverse range of cancer types. Because EBV persists in the B cells of the asymptomatic host, it can easily be envisaged how it contributes to the development of B-cell lymphomas. However, EBV is also found in other cancers, including T-cell/natural killer cell lymphomas and several epithelial malignancies. Explaining the aetiological role of EBV is challenging, partly because the virus probably contributes differently to each tumour and partly because the available disease models cannot adequately recapitulate the subtle variations in the virus–host balance that exist between the different EBV-associated cancers. A further challenge is to identify the co-factors involved; because most persistently infected individuals will never develop an EBV-associated cancer, the virus cannot be working alone. This article will review what is known about the contribution of EBV to lymphoma development.
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Keywords: Epstein–Barr virus; Burkitt lymphoma; Hodgkin lymphoma; diffuse large B-cell lymphoma

Received 31 July 2014; Revised 1 October 2014; Accepted 5 October 2014

No conflicts of interest were declared.

Introduction

EBV was discovered in the 'African' (also known as 'endemic'/high incidence) form of Burkitt lymphoma (BL), and its oncogenic credentials were confirmed when it was shown to transform resting B cells *in vitro* [1]. However, EBV was also shown to asymptomatically infect most of the world's adult population, EBV having evolved to survive in B cells for the life of infected individuals [2]. These observations pointed to the requirement for additional factors in BL pathogenesis. George Klein's laboratory showed the consistent presence in BL of one of three chromosome translocations, all of which deregulate c-myc expression [3–5]. Because *MYC* translocation is also found in EBV-negative BL and is required to sustain the high rate of proliferation characteristic of BL, it is considered the major transforming event [6], whereas EBV probably provides survival signals necessary to override c-myc-induced apoptosis [7–9]. A further pathogenic factor in endemic BL is *Plasmodium falciparum* infection [10–13]. Unravelling the complex relationships between EBV, deregulated c-myc, and *P. falciparum* has revealed important insights into BL pathogenesis.

EBV is also associated with the development of other lymphomas, including classical Hodgkin lymphoma (cHL), diffuse large B-cell lymphoma (DLBCL), and natural killer (NK)/T-cell lymphoma. Although we know less about how EBV contributes to these other malignancies, the virus clearly expresses different forms of latency in these tumours. As we will see later, variations in latent gene expression between different tumours have been used to provide a conceptual framework around which different roles for EBV in lymphomagenesis have begun to emerge. To begin to understand how EBV might contribute to lymphoma development, we will first consider the biology of EBV infection.

EBV infection in the asymptomatic host

EBV is transmitted by oral transfer; infectious virus is shed intermittently at low levels in oropharyngeal secretions. EBV shedding can also be detected in cervical secretions [14]. Primary infection is usually asymptomatic or causes infectious mononucleosis (IM) [15]. In primary infection, EBV infects B lymphocytes of the oropharyngeal mucosa, possibly after an initial transient burst of replication in the oropharyngeal epithelium. EBV resides mainly in the long-lived memory B cells of infected individuals. How the virus gets there can

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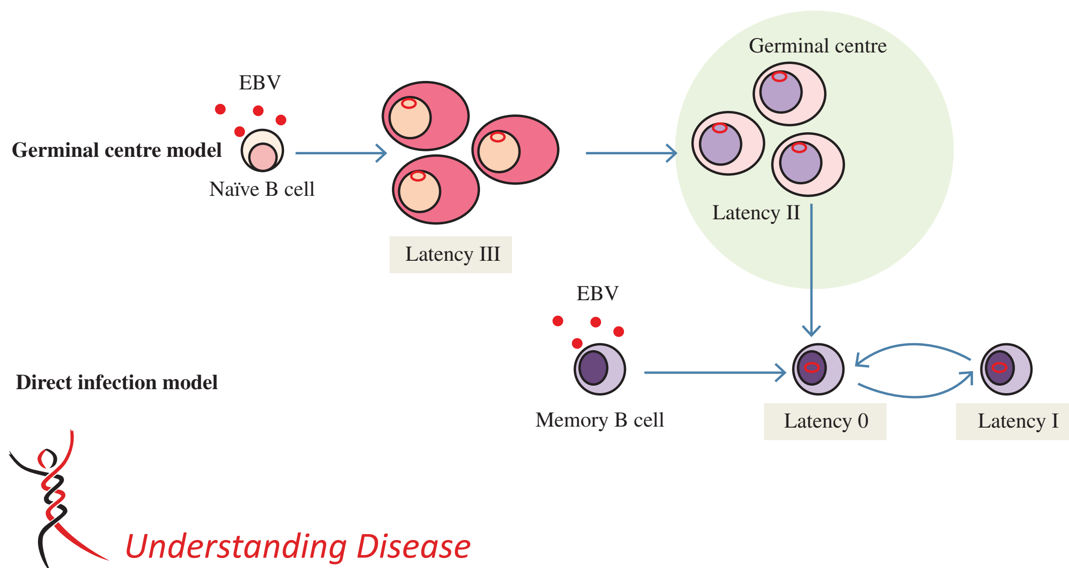

Figure 1. Two models of the EBV life cycle in the B-cell system. In the 'germinal centre' model, EBV infection of naïve B cells leads to a latency III programme which drives cell proliferation, leading to the expansion of the infected cell pool. The EBV-infected B cells then enter a germinal centre reaction and switch to a latency II programme which provides the signals for survival in the GC and differentiation to memory B cells. EBV-infected memory B cells down-regulate latent gene expression (latency 0) to avoid immune recognition. When EBV-infected cells divide, they switch on EBNA1 expression, required for the segregation of viral episomes to daughter cells during cell division; this additional form of latency is known as latency I. The 'direct infection' model proposes that EBV directly infects memory B cells.

be explained by two, not necessarily mutually exclusive, models [16,17] (Figure 1).

The 'germinal centre' model of virus persistence

This model proposes that EBV-infected memory B cells are generated by the process of normal B-cell differentiation involving germinal centres (GCs) [18]. GCs are lymphoid structures where antigen-exposed B cells undergo proliferation, class switch recombination, and somatic hypermutation (SHM) in their immunoglobulin genes – processes critical for antigen selection, affinity maturation, and choice of immunoglobulin class [19,20]. T-cell help through the CD40 receptor and antigen activation of the B-cell receptor (BCR) positively select antigen-specific B cells and drive their emergence from the GCs as either memory B cells or plasma cells [20].

In the GC model, initial infection of naïve B cells drives proliferation and expansion of the EBV-infected B-cell pool, a process thought to be analogous to that observed when B cells are transformed by EBV *in vitro*. EBV-transformed cells express the virus latency III or growth programme characterized by expression of nuclear antigens (EBNAs 1, 2, 3A, 3B, 3C, and - LP), latent membrane proteins (LMPs 1, 2A, and 2B), two groups of viral miRNA, and the non-coding Epstein–Barr-encoded RNA (EBER) [21,22]. A proportion of EBV-transformed B cells enter the GC (Figure 1) and express the latency II or default programme in which EBNA1, LMP1, and LMP2, but not the other EBNAs, are expressed [18,23–27]. LMP1 and LMP2 are functional homologues of CD40 and BCR signalling, respectively, and probably provide the signals necessary for the survival of EBV-infected B cells in the GC and their subsequent exit from the GC as memory cells [28–35].

EBV-infected memory B cells down-regulate latent gene expression (referred to as latency 0) to avoid recognition by EBV-specific immune cells. When the EBV-infected cells divide as part of normal memory B-cell homeostasis, they switch on the EBNA1 protein that is required for the segregation of viral episomes to daughter cells during cell division. This form of latency resembles that observed in most cases of EBV-positive BL and is known as latency I [36]. Activation of EBV-infected memory B cells can lead to their differentiation to plasma cells, a process that switches on the EBV lytic cycle and leads to virion release [37].

The 'direct infection' model

The rare EBER-expressing cells isolated from the GCs of patients with IM have been shown to carry somatically mutated immunoglobulin genes without evidence of intraclonal diversity [38]. In other words, these cells are apparently not undergoing SHM which might be expected if they were participating in the GC reaction. Furthermore, LMP1 protein was found only in EBV-infected cells outside, but not within GCs [39]. Two interpretations were suggested to explain these data: (1) GC B cells are directly infected by EBV but subsequently switch off SHM while continuing to proliferate; (2) EBV directly infects memory B cells and drives them to proliferate; the resulting clones enter the GC without taking part in the GC reaction [38].

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EBV has also been detected, albeit at lower levels, in a second distinct memory population, known as 'non-switched' memory B cells [40]. Unlike the generation of conventional memory B cells described above, non-switched memory B cells are apparently not dependent on GC activity, as evidenced by their presence in certain GC-null immunodeficiency states, such as X-linked lymphoproliferative disease [41,42]. Thus, in some scenarios, EBV may be able to impose a memory genotype without the requirement for a GC reaction.

Most rare EBER-positive cells detected in an otherwise EBV-negative GC might not be participating in the GC reaction, but this does not mean that GC reactions involving EBV-infected B cells do not occur. It may be that this is such an infrequent event as to be mostly undetectable in tissue sections [38]. We and others have reported instances of reactive lymphadenopathy with expansions of EBV-positive cells within one or more GC [43–48] (Figure 2). This phenomenon is more commonly observed in patients with an underlying immunodeficiency, such as HIV infection, or in adult late-onset EBV-associated B-cell lymphoproliferations associated with an age-related decline in EBV-specific immunity [48]. These expansions may represent the rare detection of EBV-infected B cells undergoing a GC reaction, although whether LMP1 is involved remains unclear since we and others have failed to detect LMP1 protein in these expanded EBV-positive GCs [43]. The more frequent detection of these lesions during HIV infection and in other immunodeficiency states might implicate the immune response in controlling the proliferation of EBV-positive GC B cells. Alternatively, in the context of HIV infection, it could reflect hyperstimulation of EBV-positive GC B cells (see later). Expansions of EBV-positive GC B cells have been found in association with EBV-positive cHL, so it cannot be ruled out that they also represent an early stage in the evolution of cHL [43,46,47].

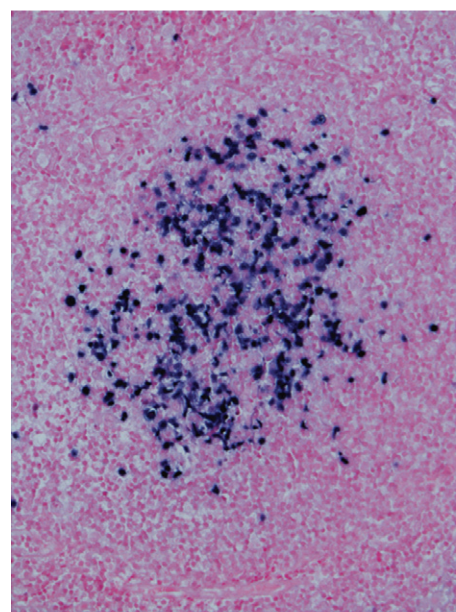

Figure 2. Expansion of EBV-positive cells in a non-malignant germinal centre. An example of the rare occurrence in germinal centres of expansions of EBV-positive cells, shown here by *in situ* hybridization. This condition is more common in patients who are immunosuppressed or in patients with a pre-existing lymphoma and could represent an exaggerated form of natural persistent infection.

EBV-associated B-cell lymphomas

EBV-positive B-cell lymphomas might be thought of as rare accidents of EBV's colonization of B cells. Most display evidence of SHM and so may have arisen from cells that have been through a GC reaction [13] (Figure 3). Alternatively, EBV might itself induce SHM (discussed later). The pattern of virus latency observed in B-cell lymphomas might be taken as evidence of the stage of B-cell differentiation from which the tumour is derived. For example, the malignant Hodgkin/Reed–Sternberg (HRS) cells of cHL express a latency II pattern [49–51] and on this basis might be considered to originate from an EBV-infected GC B cell possibly *en route* to memory [52]. On the other hand, although EBV-positive BL cells have a morphology and gene expression profile similar to EBV-infected GC B cells, they express a latency programme resembling memory B cells [53,54]. An additional feature common to EBV-associated B-cell tumours is the potential involvement of chronic immune stimuli in their pathogenesis. Although this is exemplified by the existence of rare EBV-positive tumours, such as pyrothorax- and chronic osteomyelitis-associated lymphomas, arising at sites of long-term persistent inflammation, a body of evidence suggests that immune stimuli are also involved in the development of the more common EBV-associated tumours, such as BL [55,56].

Burkitt lymphoma

BL occurs not only in its endemic form, but also at a lower incidence throughout the world (known as 'sporadic' BL), and in an HIV-associated form. Almost all endemic BL is EBV-positive, with lower (~10–15%) and intermediate (~40%) rates in sporadic and HIV-associated forms, respectively [6,57]. All forms harbour a reciprocal chromosome translocation affecting the *MYC* gene on chromosome 8 and one of the immunoglobulin heavy or κ and λ light chain loci on chromosome 14, 2 or 22, respectively, bringing the *MYC* oncogene under the transcriptional control of an immunoglobulin locus [58]. The resulting overexpression of c-myc drives the high proliferation of BL cells [59].

Breakpoints in the immunoglobulin genes in endemic BL mainly occur in the VDJ or VJ regions, whereas

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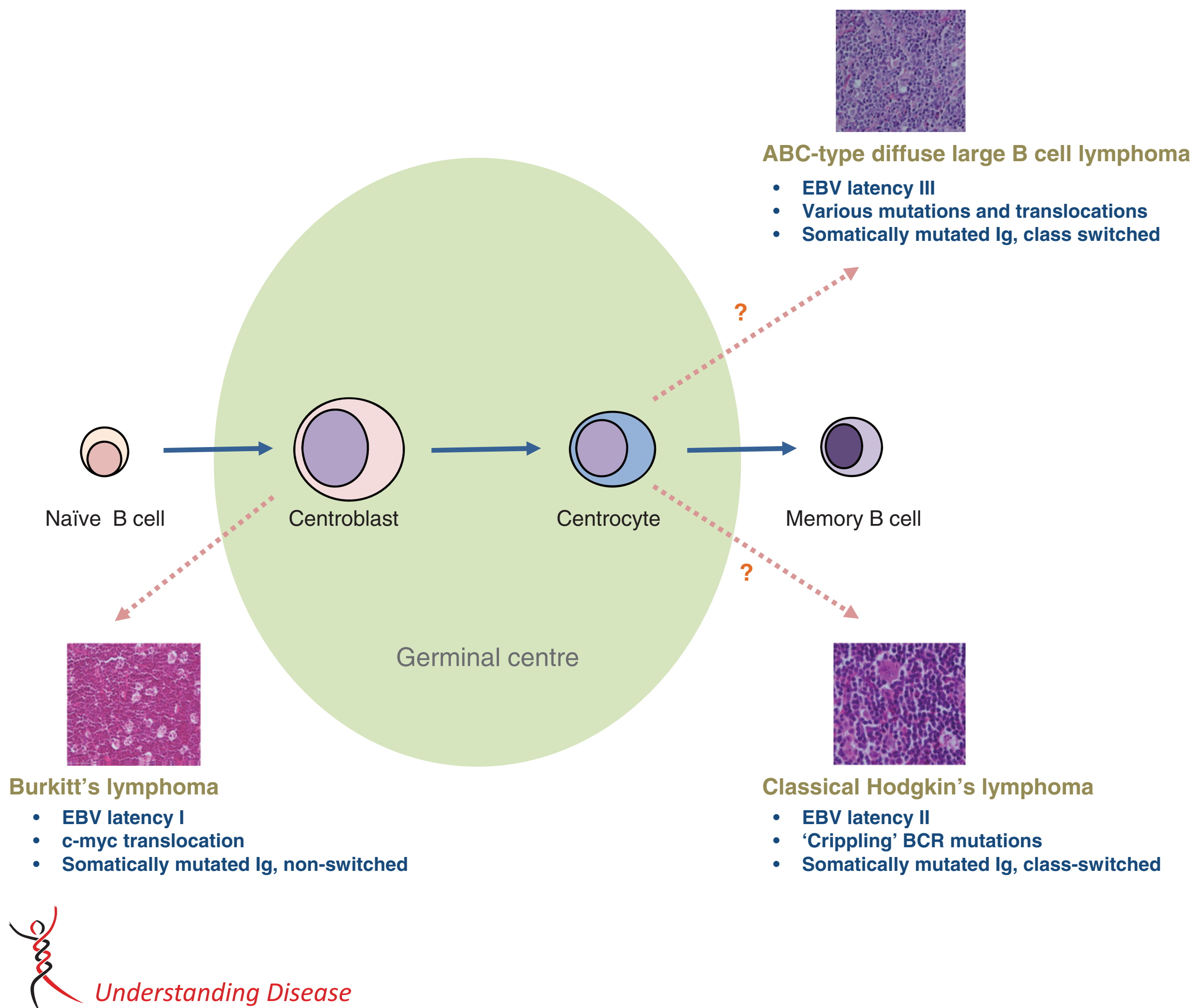

Figure 3. The derivation of the major EBV-positive B-cell lymphomas. EBV-positive B-cell lymphomas are believed to derive from cells that have the characteristics of different subsets of GC B cells. BL phenotypically resembles the proliferating centroblasts of the germinal centre, but most cases have a virus latency profile similar to memory cells. All cases carry c-myc aberrations, mostly translocations. Some cases of cHL have destructive BCR mutations, and all EBV-positive cases display a latency II programme. Most EBV-positive DLBCLs are of the activated B-cell (ABC) type and display a latency III programme similar to that observed following the transformation of B cells *in vitro*. However, the precise stage of B-cell differentiation from which each of these tumours derives is unknown.

those found in sporadic cases are commonly found in the switch region (reviewed in ref 6). This suggests that the breakpoints in endemic cases occur earlier during B-cell differentiation (ie in the bone marrow) than in sporadic tumours (ie in the GC, where class switching occurs). However, other evidence suggests that the VDJ/VJ breakpoints arise as a consequence of the aberrant activity of activation-induced deaminase (AID), the enzyme responsible for SHM in normal GC B cells, suggesting that the breakpoints in endemic cases might also occur in the GC [60]. Furthermore, AID could contribute to BL pathogenesis by inducing 'off-target' mutations in genes such as *MYC*, *BCL6*, and *FAS* (CD95) [6,61–64]. EBV infection and LMP1 expression can induce AID expression and activate SHM, potentially leading to the generation of pathogenic mutations in BL, although this effect is apparently counteracted by latency III infection and in particular EBNA2 expression [31,65–67]. The frequency of SHM is also higher in EBV-positive than in EBV-negative memory cells and in endemic and AIDS-BL than in sporadic BL [68,69]. However, one must recall the evidence presented earlier that EBER-positive cells in the GCs of IM patients are not undergoing SHM and so it is not clear if EBV induces AID expression and SHM *in vivo* [38].

The overexpression of c-myc not only drives cell proliferation but also induces apoptosis, so the BL progenitor must acquire a second independent event to overcome this [70]. The first evidence that EBV contributes to this anti-apoptotic function came from the demonstration that BL-derived cell lines that have lost viral episomes in culture are more sensitive to apoptosis than their EBV-positive counterparts [71]. In latency I, characteristic of most BLs, the viral promoter, Qp, drives expression of only EBNA1 [53]. Although important for virus episome maintenance and virus

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promoter regulation, EBNA1 can also mediate some of the anti-apoptotic effects of EBV in BL cells [72]. The restricted pattern of virus latency observed in BL is important in maintaining the BL phenotype since forced expression of the latency III programme in BL cells was shown to antagonize c-myc-driven oncogenesis [73,74].

Variant forms of BL have been described in which Qp is silenced and Wp drives expression of EBNA1, EBNA-3A, EBNA-3B, EBNA-3C, and EBNA-LP [7,75,76]. However, the full latency III programme is suppressed through deletion of the EBNA2 gene. Wp-using BLs are less sensitive to apoptosis than conventional BLs, an effect that has been attributed to the down-regulation of the pro-apoptotic molecule Bim by EBNA3A and EBNA3C, and to the overexpression of the viral bcl-2 homologue BHRF1 [77,78].

The very high incidence of EBV-positive BL in areas of holoendemic *P. falciparum* malaria can be explained by several mechanisms. First, there is some evidence of loss of T-cell control to EBV latent and lytic antigens in individuals chronically exposed to *P. falciparum* infections. This is supported by recent evidence showing that malaria can induce functional exhaustion of T cells (reviewed in ref 79). Second, malarial antigens can cause an intense polyclonal B-cell activation and induce the EBV lytic cycle, both of which could lead to the expansion of the EBV-infected B-cell pool, in turn increasing the chances of one or more of these cells accidentally acquiring *MYC* translocation [13,80]. For further details of these mechanisms the reader is referred to several excellent reviews [81,82].

Classical Hodgkin lymphoma

EBV is present in a subset of cHLs, being detectable more frequently in the mixed cellularity form in males, Asians, and Hispanics than in whites or blacks; and in the UK, in South Asian children than in non-South Asian children [83,84]. In developed countries, the proportion of EBV-positive cases is lower in young adults but higher in children, especially in those under 10 years of age. EBV-positive disease is also more frequent in elderly patients, an effect that is attributed to a decline in EBV-specific immunity with advancing age [85,86].

HRS cells display evidence of SHM, but lack a functional BCR [87]. In about a quarter of cases, loss of BCR function is caused by mutations that destroy the coding capacity of originally functional immunoglobulin genes (so called 'crippling' mutations) [88]. Thus, HRS cells are derived from GC B cells which have failed to undergo the apoptosis that would be the normal fate of GC B cells lacking a functional BCR. Two pieces of evidence support a role for EBV in providing this anti-apoptotic function. First, crippling mutations in immunoglobulin genes are almost exclusively found in EBV-positive cases [89]. Second, EBV can efficiently immortalize BCR-negative GC B cells *in vitro*, an effect that is dependent on BCR-like signalling provided by LMP2A [90–92]. LMP1 may also contribute to the survival of HRS cell precursors by constitutively activating several of the pathways, including NF-κB, JAK/STAT, and phosphatidylinositol 3-kinase/AKT, known to be aberrantly activated in HRS cells [93–95]. However, EBV latent gene expression in GC B cells might not only contribute to anti-apoptotic properties but also interfere with the normal GC B-cell differentiation programme [29,34,96,97].

EBV-positive post-transplant lymphoproliferative disease

In healthy asymptomatic carriers, EBV-induced transformation is suppressed by an EBV-specific immune response mainly targeting EBNA3 proteins. Impairment of this response can lead to the uncontrolled expansion of EBV-transformed B cells, best exemplified by the EBV-positive B-cell tumours that arise soon after solid organ or haematopoietic stem cell transplantation, when patients are heavily immunosuppressed (reviewed in refs 98 and 99). These EBV-driven tumours are members of a heterogeneous group of conditions, collectively known as post-transplant lymphoproliferative disorders (PTLDs). There is evidence of SHM in most of these tumours, indicating their GC or post-GC B-cell origin [100]. They often regress following the withdrawal of immune suppression and respond very well to adoptive T-cell therapy [101,102] (and reviewed in ref 98). Other forms of PTLD, not all of which are EBV-positive, arise several years or more after solid organ transplantation in patients on low-level immunosuppression for life [103].

Other B-cell lymphomas

EBV is also present in other B-cell lymphomas, including those classified as diffuse large B-cell lymphoma (DLBCL). DLBCL is a heterogeneous group of malignancies that can be subdivided on the basis of different gene expression profiles and mutational signatures into two major subgroups: germinal centre B-cell (GCB) and activated B-cell (ABC) forms. Most EBV-positive cases are of ABC type [104–107]. EBV is usually present in DLBCL only in the setting of immune impairment. For example, EBV-positive DLBCLs make up around 30–50% of the late-onset post-transplant tumours described above and approximately 30% of AIDS-DLBCLs (many of which are of the so-called 'immunoblastic' type) [108,109]. Most EBV-positive DLBCLs express either a type II or, more frequently, a type III form of latency. The EBNA3 proteins are expressed in latency III and may contribute to lymphoma development. For example, EBNA3A and EBNA3C are potential oncogenes, which can repress transcription of pro-apoptotic and senescence-inducing genes [77,110,111]. On the other hand, EBNA3B has recently been reported to have tumour suppressor functions in

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EBV-infected B cells, and its loss of function could be important for DLBCL [112].

The recognition that EBV-positive DLBCL can also arise in older patients without a prior history of immune suppression has led to the designation of a new provisional entity, referred to as 'EBV-positive diffuse large B-cell lymphoma of the elderly' [113,114]. This condition might be due to senescence of the EBV-specific immune response associated with advancing age (reviewed in ref 107). EBV-positive DLBCL has also been described in apparently immunocompetent younger patients including children [115,116]. An important area of future research will be to define the precise nature of the immunological defects present in patients with EBV-positive DLBCL.

HIV, the immune system, and EBV-associated lymphomagenesis

The incidence of some EBV-associated lymphomas is increased during human immunodeficiency virus (HIV) infection. Analysis of these tumours has provided unique insights into how EBV, HIV, and the immune system co-operate in lymphomagenesis. BL occurs early in HIV infection when circulating CD4+ T-cell numbers are normal or only slightly decreased. In contrast, the incidence of the 'immunoblastic' form of DLBCL is increased only when circulating CD4+ T-cell numbers fall and the patient is severely immunocompromised. In accordance with these observations, the incidence of AIDS-BL has not dramatically declined in the era of highly active retroviral therapy, unlike that of AIDS-DLBCL [117–121].

Thus, immune impairment is the major driver in some HIV-associated lymphomas (eg immunoblastic DLBCL), but to a lesser extent, if at all, in others (eg BL). What additional factors could account for the initiation of BL during HIV infection? In its earliest stages, HIV infection is characterized by an expansion of GC activity and intense polyclonal B-cell activation [122,123]. This is believed to increase the pool of EBV-infected B cells carrying accidental c-myc/Ig translocations. As CD4 counts fall, GC activity declines and the incidence of BL decreases [124]. Therefore, HIV could contribute to BL pathogenesis in a manner analogous to that described above for *P. falciparum* infections (reviewed in ref 13).

In contrast, the incidence of HL is only 5–15 times higher among people with HIV and AIDS compared with the general population [125–127]. Furthermore, HL is more common in HIV-infected patients with intermediate levels of immune impairment; this is reflected in relatively lower rates for severely immunocompromised AIDS patients [126]. Two interpretations have been proposed to explain these findings: first, at very low CD4+ T-cell counts, the morphological presentation of HL shifts to an appearance more similar to non-Hodgkin lymphoma (in which there are fewer CD4+ T cells in the microenvironment), resulting in a diagnostic misclassification; or second, CD4+ T cells have a tumour-promoting function in cHL.

EBV and the lymphoma microenvironment

cHL is a particularly good example of the importance of the tumour microenvironment in lymphoma development. cHL is rich in CD4+ T cells and other inflammatory cells, which surround the malignant cells and support their growth and survival. HRS cells secrete CCL5 (RANTES), CCL17 (TARC), CCL20, and CCL22, which can attract helper and regulatory CD4+ T cells [128–131]. CCL5 also attracts eosinophils and mast cells. The secretion of IL-8 by HRS cells recruits neutrophils [128]. HRS cells also activate fibroblasts, which in turn produce eotaxin and CCL5, thus further contributing to the attraction of eosinophils and T regulatory cells [132,133]. EBV proteins, particularly LMP1, contribute to this microenvironment by stimulating the production by HRS cells of many of these cytokines and chemokines [34,131,134] (reviewed in ref 135). HRS cells also produce immunosuppressive factors including IL-10, galectin 1, TGFβ, and PD1L, all of which can potentially inhibit cytotoxic T-cell responses directed to EBV-infected HRS cells [136–142]. In turn, the cHL microenvironment provides survival signals to EBV-positive HRS cells mediated by various ligand–receptor interactions including CD40–CD40L, CD30–CD30L, APRIL–BCMA, and NGF–TRKA [143,144].

Regulation of EBV gene expression and function by the microenvironment

Also prominent in many cases of cHL is an abundance of collagen [145–148]. Collagen is not only a structural component but also an important signalling molecule [149]. Recently, we reported that LMP1 can induce expression of the collagen receptor, discoidin domain receptor 1 (DDR1), in B cells [148]. Exposure of DDR1-expressing B-cell lymphomas to collagen protected them from apoptosis, suggesting that some of LMP1's oncogenic effects may be dependent on alterations to the microenvironment [148].

As well as potentially modifying the functions of individual EBV proteins, there is evidence that the microenvironment can also modulate the pattern of virus gene expression. For example, IL-21 and IL-2 together with CD40 ligation, all present in the GC, can down-regulate EBNA2 and up-regulate LMP1 expression [150,151], imposing a type II latency pattern akin to that observed in cHL. Furthermore, our recent work has identified a significant role for Notch ligation in the regulation of LMP1; activated Notch inhibits LMP1 expression from the conventional LMP1 promoter initiated by EBNA2 during primary B-cell infection [152].

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NK/T-cell lymphomas

EBV is also associated with lymphomas of non-B cells, including extra-nodal NK/T-cell lymphoma, nasal type (ENKL) [153]. ENKL is a rare, aggressive tumour that is most common in Asian and Latin American populations. The presence of EBV in NK/T tumours is diagnostic. However, while the mechanism of EBV is unknown, accidental infection of NK or T cells is suspected; some tumours have a cytotoxic phenotype, demonstrated by expression of T-cell intracytoplasmic antigen-1 and granzyme B, suggesting that they arose following the infection of CTLs during the killing of EBV-infected cells [154,155]. NK/T-cell tumour cells produce cytokines that are responsible for the symptoms characteristic of these tumours and of related disorders [chronic active EBV infection (CAEBV) and fatal haemophagocytic syndrome] [156]. NK/T-cell lymphomas express a latency II pattern with variable LMP1expression, which contributes to the excessive production of pro-inflammatory cytokines mediated by NF-κB activation [156].

Conclusions

In most tumours that arise in severely immunocompromised individuals, EBV is the main driver of tumour growth. However, in BL and HL, EBV provides an anti-apoptotic function that complements c-myc deregulation or loss of BCR functions, respectively. In BL, chronic immune stimulation, induced either by HIV or by *P. falciparum*, or by both, might increase the pool of EBV-infected GC B cells with *MYC* translocation. In cHL, EBV contributes to the chronic inflammatory milieu that surrounds and supports the tumour cells. Emerging evidence suggests that this chronic inflammatory microenvironment not only might regulate virus gene expression but could also promote EBV's oncogenic functions.

Acknowledgments

MV, KV, and PGM were supported by Leukaemia Lymphoma Research and L-FY was supported by the University of Malaya (UM.C/625/1/HIR/MOHE/DENT/23). We thank Ghada Mohamed, Maha Ibrahim, and Patrik Flodr for pathology expertise and Eszter Nagy for critical reading of the manuscript.

Author contribution statement

All authors contributed to the writing of the paper.

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The Pathological Society

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