HHS Public Access

Author manuscript

Adv Exp Med Biol. Author manuscript; available in PMC 2018 July 19.

Published in final edited form as:

Adv Exp Med Biol. 2017 ; 1018: 57–74. doi:10.1007/978-981-10-5765-6_5.

Current Progress in EBV-Associated B-Cell Lymphomas

Yonggang Pei, **Alexandria E. Lewis**, and **Erle S. Robertson**

Department of Otorhinolaryngology-Head and Neck Surgery, and Microbiology, Tumor Virology Program, Abramson Comprehensive Cancer Center, Perelman School of Medicine at the University of Pennsylvania, 3610 Hamilton Walk, 201E Johnson Pavilion, Philadelphia, PA 19104, USA

Abstract

Epstein-Barr virus (EBV) was the first human tumor virus discovered more than 50 years ago. EBV-associated lymphomagenesis is still a significant viral-associated disease as it involves a diverse range of pathologies, especially B-cell lymphomas. Recent development of high-throughput next-generation sequencing technologies and in vivo mouse models have significantly promoted our understanding of the fundamental molecular mechanisms which drive these cancers and allowed for the development of therapeutic intervention strategies. This review will highlight the current advances in EBV-associated B-cell lymphomas, focusing on transcriptional regulation, chromosome aberrations, in vivo studies of EBV-mediated lymphomagenesis, as well as the treatment strategies to target viral-associated lymphomas.

Keywords

Epstein-Barr virus; Latent infection; B-cell lymphomas

5.1 Introduction

Approximately two million new cases of cancer are annually attributed to infectious agents. 12% to 15% of human cancers are associated with oncogenic virus infection and are suspected to be major drivers [1, 2]. Uncovering the roles of infectious agents will help facilitate our understanding of the mechanism of cancer pathogenesis mediated by infectious agents and develop potential methods for therapeutic intervention. Epstein-Barr virus (EBV), also known as herpesvirus 4, was the first human tumor virus to attract significant attention since it was discovered associated with Burkitt's lymphoma in 1964 [3]. EBV infects more than 95% of the world's population and sustains lifelong asymptomatic infection. Its ability to induce oncogenesis is likely due to suppression of the immune system or a result of the uncontrolled proliferation. A recent study demonstrated that 1.8% of cancer deaths were related to EBV-attributable malignancies worldwide [4].

Initial infection of EBV is usually asymptomatic or can cause infectious mononucleosis (IM) [5]. The following lytic infection in epithelial cells results in the expression of the

Correspondence to: Erle S. Robertson.

complete viral gene program. Previous studies clearly showed that EBV had the ability to transform human primary B lymphocytes into lymphoblastoid cell lines (LCLs) [6, 7]. To date, EBV is still the most efficient transforming virus in culture and can rapidly transform resting B cells in vitro [8, 9]. The persistence of EBV infection is mainly in B cells and leads to EBV associated B-cell lymphoma, typically in individuals with suppressed immune systems. Nasopharyngeal carcinoma (NPC) and EBV-associated gastric carcinoma (GC) are also related with EBV-infected epithelial cells, but whether or not the virus is a major contribution to the pathogenesis of these tumors is still unclear. Therefore, the presence and precise contributions of EBV to numerous human cancers is a challenge to explain. However, it also provides a great opportunity to the development of novel prophylactic or therapeutic methods.

5.2 EBV-Associated B-Cell Lymphomas

5.2.1 Burkitt's Lymphoma (BL)

Burkitt's lymphoma (BL) can be classified into three forms based on the geographic distribution: endemic BL (eBL), sporadic BL (sBL), and HIV-associated BL [10]. The discovery of EBV in BL tumors and the fact that almost 100% of endemic BL are EBV positive support the possibility that BL tumors are driven by EBV as a major contributor. Further sera-epidemiological studies have provided evidence that African BL tumors are positive for EBV [11]. One critical feature of BL tumors is the translocation and activation of *MYC* [10]. MYC overexpression in BL tumors results from a translocation event between the *MYC* gene and immunoglobulin locus which further regulates the downstream network and facilitates tumorigenesis [12, 13]. Most EBV-positive BL tumors consistently express latent antigen EBNA1 as the predominant latent antigen and are termed latency I [14]. Previous studies show that EBNA1 can play antiapoptotic roles which also contributes to increased tumorigenicity [15, 16]. In addition, and different from that observed in Africa, only 15–20% of BL tumors are EBV positive in other parts of the world [12]. The extremely uncommon observation is consistent with the fact that EBV together with malaria can increase the frequency of BL tumors. However, the mechanism of their interaction is not fully understood and needs further investigation [12, 17].

5.2.2 Diffuse Large B-Cell Lymphoma (DLBCL)

Diffuse large B-cell lymphoma (DLBCL) is the most common non-Hodgkin lymphoma (NHL), accounting for 40% of adult NHL [18]. Two major subtypes of DLBCL, germinal center B cell (GCB) and activated B cell (ABC), were divided based on genomic signatures [19]. Approximately 10% DLBCL is EBV positive, which has been described in the World Health Organization (WHO) classification system [20]. EBV-positive DLBCL is mainly identified in the elderly because the median age of these patients is 71 years, although in younger patients can also be found [20, 21]. The incidence of EBV among DLBCL patients is less than 5% in the United States and European countries but 10–15% in Asian and Latin American countries [21–24]. EBV-positive DLBCL is associated with activation of NF-κB and JAK/STAT signaling pathways, but the detailed mechanisms of tumorigenesis will need to be further investigated [25].

5.2.3 Posttransplant Lymphoproliferative Disease (PTLD)

Posttransplant lymphoproliferative disease (PTLD) is mainly derived from B cells in transplant patients [26, 27]. It is often associated with EBV infection in the context of an impaired immune surveillance system. Furthermore, 60–80% of PTLDs are shown to be EBV positive [28]. EBV is the crucial driver of PTLDs development that is typically early-onset cases of posttransplantation [29]. Early-onset PTLDs that are associated with EBV-infected B cells are usually polyclonal or oligoclonal, while most late-onset PTLDs with or without EBV infection are monoclonal [30]. The transplant-associated immunosuppression in PTLDs leads to expression of EBNA3 family members in addition to all the latent antigens, which are characteristics of latency III-associated EBV infection [9]. The prevention and treatment of EBV-associated PTLDs rely on surgery with irradiation, immunotherapy with monoclonal antibodies (e.g., rituximab), and antiviral drugs [31]. The development of T-cell-based therapies has been very promising to treat EBV-driven PTLDs by transferring patient-derived ex vivo amplified EBV-specific cytotoxic T cells back to patients [32].

5.2.4 Hodgkin Lymphoma (HL)

Hodgkin lymphoma (HL) is characterized by the presence of Hodgkin-Reed-Sternberg (HRS) cells [33]. The direct link of EBV and HL is confirmed by the detection of EBER expression in HRS cells using EBER-specific in situ hybridization [34]. In addition, EBNA1, LMP1, and LMP2A are also expressed in EBV-infected HRS cells [35]. HL cells are B-cell originated and derived from the germinal center. They require the necessary signals to escape apoptosis as a result of the lack of functional BCRs [36]. Therefore, in EBV-infected HRS cells, LMP1 mimics the CD40 receptor, recruits TRAF family members, and further activates downstream NF-κB signaling pathways to promote cell survival by inhibiting cell apoptosis [37]. Meanwhile, LMP2A recruits cytoplasmic kinase to activate B-cell Ig receptors or activates the PI3K-AKT pathway in the absence of Ig receptors to promote B-cell survival and growth [9, 38].

5.2.5 EBV-Associated B-Cell Lymphoma in the Context of HIV

The increased reports of EBV-associated lymphomas with the onset of acquired immunodeficiency syndrome (AIDS) imply a molecular connection between EBV and HIV in the infected hosts [39]. In HIV-associated lymphomas, EBV infection can be found in 80% of DLBCL and 80–100% of primary central nervous system lymphomas (PCNSL) [40]. BL can occur before HIV infection even if circulating CD4+ T-cell numbers are normal. DLBCL typically occurs only after HIV infection when circulating CD4+ T cells are exhausted [41]. AIDS-BLs involve the typical *MYC* translocation and are less frequently infected by EBV [42, 43]. These observations suggest that HIV may be a potential stimulator which leads to an increase in the risk of EBV-mediated *MYC* translocation and therefore lymphomagenesis. Most AIDS-associated lymphomas that are EBV positive do express broad expression of the latent antigens and are type III latency program. This is likely due to the suppressed immune system and so a loss of control of the EBV-positive cells.

5.3 Molecular Biology of EBV-Mediated B-Cell Lymphomas

EBV is an oncogenic herpesvirus because of its ability to immortalize human primary B lymphocytes in vitro. In general, EBV primary infection is asymptomatic, and the following persistent infection will be established in memory B cells after an early period of virus production [44]. Therefore, two typical EBV infections can be established in the host: lytic infection in epithelial cells and latent infection in memory B cells [45, 46]. The initial events of EBV primary infection are the focus of current studies, but the detailed mechanisms are still not completely understood. In latent infection, specific transcription programs are defined as latency I, II, and III according to the expression of the viral-encoded latent antigens, which are thought to be the critical drivers of EBV-associated lymphomagenesis.

5.3.1 EBV-Associated Transcription Regulatory Network

One hallmark of cancer is the dysregulation of gene expression [47]. The characteristic of effective in vitro transformation by EBV indicates its strong ability to regulate cellular transcriptional programs. With the rapid development of high-throughput sequencing technologies, more and more studies are focused on a complicated regulatory network during EBV-mediated B-cell transformation by utilizing the common database such as NCBI GEO, ENCODE, and TCGA project [48–50].

To determine the molecular mechanisms which drive lymphomagenesis, EBV-transformed lymphoblastoid cell lines (LCLs) are one of the best systems to perform in vitro studies. More recent studies have concentrated on EBV latent protein-mediated regulatory networks using next-generation high-seq analysis, of which the frequently used is ChIP-seq (Table 5.1). ChIP-seq analysis indicated that EBNA2 can convert B lymphocytes to LCLs by targeting H3K4me1 modified sites as well as noncoding regions to regulate cellular gene expression to drive proliferation of LCLs [51]. In addition, EBNA2 induces a new pattern of genome-wide binding through recruitment of RBPJκ and EBF1 to drive LCL survival [52]. EBNA2 recruits the SWI/SNF ATPase BRG1 to bind large-scale *MYC* enhancers activating its expression [53]. EBNA-LP binds with B-cell transcription factors (TFs), which are highly similar to EBNA2 including RBPJκ and EBF [54]. These high-seq data provides evidence to support the explanation that both EBNA2 and EBNA-LP are crucial for LCL outgrowth. EBNA3C, another EBV latent antigen essential for LCLs growth, is associated with cellular transcription factors. It binds to BATF/IRF4 and SPI1/IRF4 sites to repress CDKN2A transcription through the recruitment of Sin3A in LCLs [55]. EBV latent proteins EBNA3A and EBNA3C inhibit BCL2L11 transcription by recruiting the H3K27 methyltransferase EZH2 to silence long-range enhancers [53]. ChIP-seq analysis shows that EBNA2 and EBNA3s (EBNA3A, EBNA3B, and EBNA3C) can target multiple cellular genes through cell-specific regulation of long-range enhancer-promoter interactions [56]. Another study indicated that while these four latent antigens can competitively bind to RBPJκ at its repressive sites to control cellular genes expression, EBNA3s are more likely to interact with other transcription factors [57]. For example, IRF4 is essential for EBNA3C to associate with specific sites on viral and cellular DNA [16, 55, 57, 58]. A recent study identified a number of host dependency factors in BL and LCLs using CRISPR/Cas9 loss-of-function screen [59]. These specific genes, including PI3K/AKT, cFLIP, BATF/IRF4, and IRF2, are

likely crucial in regulating downstream transcriptional network to facilitate cell growth and survival.

During EBV primary infection, the correlative latent antigens convert resting B cells to LCLs, and their dependent function may rely on super-enhancers to control B-cell growth [60]. EBV super-enhancers (ESEs) with higher H3K27c signals involve the oncogenes MYC and Bcl2 to promote LCL growth and survival, which provides new insights on EBV-induced lymphoproliferation [60]. EBNA2, EBNA3A, and EBNA3C can enhance RUNX3 expression via RBPJκ to regulate the upstream RUNX3 super-enhancer and meanwhile control the downstream RUNX1 expression [61]. Additionally, abundant enhancers (eRNAs) are also transcribed from ESEs and are regulated by the activity of ESEs [62]. For example, the inactivation of EBNA2 and bromodomain-containing protein 4 (BRD4) in ESEs will significantly reduce the expression of eRNAs and further the MYC protein, therefore affecting LCL growth [62].

About 300 novel EBV transcripts have been predicted by combining multiple platform data from PacBio SMART Iso-Seq, RNA-Seq, and deep-CAGE, which illustrates the complex regulation of viral gene transcription during EBV infection [63]. Studies on miRNA targetome show that EBV miRNAs mainly target cellular transcription factors to manipulate the microenvironment during latent infection, suggesting the importance of EBV-expressed miRNAs in contributing to viral-mediated oncogenesis [64]. Furthermore, EBV miRNAs can modulate immune recognition to protect infected cells from killing by cytotoxic EBV-specific $CD4^+$ T cells through repression of pro-inflammatory cytokine release, naïve $CD4^+$ T-cell differentiation, and peptide presentation, which allow for establishment of latent infection and development of lymphomas [65]. Similarly, EBV miRNAs can use multiple pathways to evade immune surveillance and killing by EBV-specific $CD8^+$ T cells [66].

Although the development and manipulation of high-throughput sequencing technologies provide us a deeper and wider understanding of EBV-mediated transformation or lymphomagenesis (Fig. 5.1), the complicated regulatory network targeted by EBV latent infection is still being explored. Furthermore, systematic proteomic analyses can possibly validate some of the genomic observations and gain additional insights into EBV-host interactions [67]. In the future, more efficient systems and more advanced technologies with higher resolution, specificity, and sensitivity will be helpful in revealing the complex EBV-host interactions in associated lymphomas.

5.3.2 Genomic Instability and Chromosome Aberrations

Genomic instability is a hallmark of cancer that increases the risks of oncogenic chromosome alterations [1, 9]. Previous studies have indicated that EBV persistent infection can result in chromosome aberrations in associated lymphomas [9, 26, 68]. EBV latent antigens play crucial roles in driving genomic instability. To be specific, EBNA1 may function to contribute to genomic instability through activation of the RAG gene or induction of reactive oxygen species (ROS) [17, 29]. EBNA3C can promote genomic instability by inhibiting BubR1 transcription and inactivating the mitotic spindle checkpoint [69]. Additionally, EBNA3C can compromise the mitotic spindle checkpoint and block caspase-mediated cell death, leading to abnormal mitosis and DNA damage accumulation

[15, 70]. Although the detailed mechanism of EBNA3C-mediated genetic instability needs further investigation, multiple functions of EBNA3C may contribute to genetic instability directly or indirectly by binding with cell cycle or DNA damage checkpoint proteins, including cyclin A [71], Chk2 [72], cyclin D1 [73], p53 [74, 75], and the E2F family member E2F1/E2F6 [28, 76]. LMP1-associated genomic instability may also result from telomerase activation and DNA damage response (DDR) inhibition [69, 77]. Intriguingly, EBV tegument protein BNRF1 could also induce centrosome amplification and further chromosome instability during lytic infection, suggesting that EBV viral particles may be sufficient to modify host chromosome without the establishment of latent infection [78].

In addition, the EBV genome can frequently integrate into host cell chromosomes in persistently infected B cells [22, 79, 80]. This integration increases the possibility of lymphomagenesis when the constitutive regions release the viral genome which leads to loss of normal DNA or chromosome instability [81]. For instance, the integration of the EBV genome into chromosome 6q15 blocks the expression of the tumor repressor BACH2 in Burkitt lymphoma cell lines [80]. Using whole genome sequencing technology, a recent study reports that a comprehensive view of integration sites shows that they are randomly distributed across the entire host genome in EBV-positive Raji (Burkitt's lymphoma cells), and C666-1 (nasopharyngeal carcinoma cells) and so may be contributing to lymphomagenesis [25]. The frequent chromosome recombination, involved in chromosome 8 and c-Myc activation, is also noted in Burkitt's lymphoma cells after combined treatment with EBV and purified 4-deoxyphorbol ester [82].

5.3.3 In Vivo Models of EBV Infection

Host-range restriction is a major limitation of EBV research because humans are the exclusive natural host for EBV. Therefore, the development of a more efficient in vivo system to support the studies from in vitro results will provide additional information related to the complicated EBV-host interactions. An important achievement on in vivo system began with the development of *scid*-hu PBL mouse through the injection of human peripheral blood leukocytes (PBL) into C.B-17 *scid* mice that lack B and T cells because of the severe combined immunodeficiency (SCID) phenotype [83, 84]. Later, another *scid*-hu thy/liv mouse was generated by implanting fetal thymus, liver cells, and fetal lymph nodes into C.B-17 *scid* mice [85]. However, these mice have obvious shortcomings of generated graft versus host disease and transient immune responses [86]. Subsequently, a new series of mice models were generated to overcome the preceding disadvantages by transplanting human hematopoietic stem cells (HSCs) into various mice such as NOD/Shi-*scid* Il2rg^{null} (NOG) [87], BALB/c Rag2$^{-/-}$Il2rg$^{-/-}$ (BRG) [88], and NOD/LtSz-*scid* Il2rg$^{-/-}$ (NSG) [89]. These transplanted HSCs reconstituted the human immune system by differentiating into diversified cells, including B cells, T cells, natural killer (NK) cells, dendritic cells (DCs), monocytes, and macrophages [86].

Given the great improvement in mouse models, it is possible to further study the mechanisms of EBV-associated lymphomagenesis in vivo using humanized mice. Previous studies have shown that EBV could infect humanized BALB/c Rag2$^{-/-}$Il2rg$^{-/-}$ mice and induce specific T-cell response [88]. A mouse model for EBV infection was established by

transplanting only $CD34^+$-depleted human cord blood mononuclear cells into NOD/LtSz-*scid* $Il2rg^{-/-}$ (NSG) mice [90]. The results from this EBV-infected mouse model indicated that the PD-1/CTLA-4 blockade will induce strong specific T-cell responses and inhibit the outgrowth of EBV-associated lymphomas [90].

To further support human T cells which demonstrate HLA-restricted cytotoxic functions in mouse models, an immunodeficient NSG-HLA-A2/HHD mouse was created through the introduction of HLA-A2 allele into $CD34^+CD38^-$ HSC- transplanted NSG mice [91]. The new mouse model showed a relatively complete immune system that expresses HLA class I heavy and light chains, promotes human T-cell development, and produces functional $CD4^+$ and $CD8^+$ T cells. In this mouse model, EBV infection will result in B-cell-associated lymphoproliferative diseases, which can be inhibited by HLA-restricted CTL cytotoxicity [91]. What's more, NK cells are necessary to control infectious mononucleosis (IM) symptoms by targeting EBV lytic antigens and so control lytic infection [92]. Furthermore, NOD/SCID-hu BLT mice (or BLT mice) are developed by transplanting *scid*-hu thy/liv mice with autologous $CD34^+$ cells which combines the advantages of *scid*-hu thy/liv mice model and $CD34^+$ cell-transplanted NOD/SCID mice model [36]. BLT mice were shown to have a more complete human immune system, of which the T cells generate long-term, specific adaptive immune responses after EBV infection via human major histocompatibility complex (MHC) class I and II [36].

In 2011, an improved humanized mouse model was developed through the transplantation of human fetal $CD34^+$ hematopoietic stem cells and thymus/liver tissue into NOD/LtSz-*scid* $Il2rg^{-/-}$ (NSG) mice [93]. The mouse model supports long-term EBV latent infection and lymphoma development. Further experiments showed that EBV lytic infection was critical for B-cell lymphomagenesis with limited help of the immune system [93]. The following application of this mouse model with wild-type EBV or LMP1-deficient EBV infection demonstrated that LMP1 may not be essential for EBV-mediated lymphomagenesis but that T cells may substitute LMP1 function for development of B-cell lymphomas [94].

Different from the application of humanized mouse model, a recent study reported establishment of a transgenic mouse model with conditional LMP1/2A coexpression in germinal center (GC) B cells [95]. In this mouse model, LMP1/2A showed very limited function in immunocompetent mice, while they promote B-cell lymphoproliferative diseases in the context of T-cell or NK-cell deficiency [95].

5.4 Treatment of B-Cell Lymphomas

Diffuse large B-cell lymphoma (DLBCL) continues to be one of the few lymphomas that remain curable due to advancements made over the last decade. More than half of the patients can be cured using treatments that include chemo-, radio-, or immunotherapeutic regimens [96]. However, approximately 30–40% of patients diagnosed will develop relapsed or refractory disease after being treated for DLBCL [97, 98]. Treatment of these patients has become extremely difficult due to the resistance that has grown with the disease [99]. The improved outcome in patients with DLBCL and relapsed-refractory DLBCL (RR-DLBCL) is largely attributed to the incorporation of rituximab into standard regimens [99, 100]. With further findings and introduction of novel specific anticancer agents and therapeutic

approaches, treatment and survival of affected patients are likely to improve tremendously [101].

DLBCL is commonly treated with R-CHOP, a combination of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone, and it has shown great benefits for patients [102]. Tolerance in patients of all ages has been demonstrated, and survival rates have increased, specifically in patients diagnosed with non-Hodgkin's lymphoma [103]. Recent findings indicate that in combination with rituximab or R-CHOP, drugs lenalidomide and epratuzumab could be effective in not only first-line treatment of DLBCL but also RR-DLBCL [96]. Other novel agents such as ibrutinib, bortezomib, CC-122, and pidilizumab have been shown to be successful in the first-line treatment of DLBCL as both single agents or in combination with rituximab-based chemotherapy [96]. Studies have also investigated the role of the NF-κB/Rel family, specifically nuclear factor kappa-B (NF-κB) and RelA (p65) in DLBCL. High p65 nuclear expression is a significant adverse biomarker in patients with early-stage (I/II) DLBCL [104]. Findings have shown that with p65 inactivation, cell growth and survival can be effectively inhibited. Furthermore, activation of the JAK-STAT and NF-κB pathways is characteristic of EBV-positive DLBCL [25]. Therefore, development of therapies targeting these pathways would be of potential benefit for these patients and lead to an improvement in their post-therapy outcomes.

Another major development in the treatment of DLBCL is CAR T-cell therapy. This therapy utilizes chimeric antigen receptor (CAR)-engineered T cells specifically engineered to recognize their target antigen through the scFv-binding domain [105]. This recognition results in the activation of T cells in a major histocompatibility complex (MHC)-independent manner [106]. Investigation of this therapy has demonstrated promising outcomes by targeting CD19, CD20, or CD30 which is significant for B-cell malignancies such as B-cell non-Hodgkin's lymphoma (B-NHL) and Hodgkin's lymphoma (HL) [106]. Though still in development, success has been shown in treatment of patients, and with a deeper understanding of its functional role, the future of this novel therapy will likely prove to be promising for many diseases.

Research has led to the discovery that B-aggressive lymphoma-1 protein and ADP-ribosyltransferase BAL1/ARTD9 may serve as a novel potential drug target for treatment [96, 107]. Combining a drug(s) targeting STAT1 or the macrodomains of BAL1/ARTD9 with common day therapeutic treatments might be a successful strategy toward increasing the sensitivity of HR-DLBCL to classic therapy [107]. Several other potential therapies have been identified through other ongoing investigations including the targeting of Deltex-3-like E3 ubiquitin ligase (DTX3L) and the BET Bromodomain Protein BRD4 [1, 96, 108]. Preliminary studies indicate that DTX3L controls CXCR4, a chemokine receptor [108]. Further studies would need to be done to identify the link, if any, of DTX3L via CRCX4 with DLBCL. However, a therapy involving this control mechanism shows great potential [108]. Regarding BRD4, studies have shown that the BET inhibitors have the ability to inhibit oncogenic NF-κB activity through decreased expression of the NF-κB target genes IL6 and IL10 [1]. These findings, along with the developments in understanding the functions of NF-κB and RelA (p65), highly support the need for further research into developing a therapeutic drug targeting NF-κB complex.

Further investigation on these therapies, with or without standard immunochemotherapy, would provide major insights and pave the way to developing successful treatments for patients suffering from more aggressive types of DLBCL or RR-DLBCL or even different types of lymphomas. It is also believed that acquired drug resistance is mediated by a finite set of pathways. If these pathways can be identified and the targets that need to be suppressed or activated can be determined, sensitivity could be restored to drugs that were used successfully in a prior line of therapy or optimize the efficiency of the available therapeutic personalized regimens [13, 96].

5.5 Conclusions

EBV was discovered more than 50 years ago, but a large body of questions remain unanswered. Although EBV infects more than 90 % of the world's population, only a subset of the related infections results in lymphomagenesis. The lifelong relationships between host and EBV suggest the importance of the immune system in normal individuals. For many immunodeficient patients, EBV-induced lymphomagenesis is a frequent occurrence. Although EBV-associated lymphomas have been studied for many years, the precise roles of EBV in these processes are still unclear. EBV can infect B cells and establish latent infection, further inducing them toward lymphomagenesis under specific conditions in the microenvironment. Although the in vitro model of EBV infection has been established for many years, the detailed strategies of EBV infection, which includes latent and lytic infection, are not completely understood. The complex regulatory network is associated with regulation of numerous transcription factors, viral lytic/latent antigens, and their associated relationships. In addition, the development of NPC or GC after EBV infection has not been completely investigated because of the limitation of an efficient in vitro and in vivo model system. It is anticipated that the combined application of high-throughput next-generation sequencing technologies and in vivo mouse models will significantly improve our understanding of EBV biology in the near future and the development of potential therapeutic intervention strategies.

Acknowledgments

This work was supported by National Cancer Institute at the National Institutes of Health public health service Grants P30-CA016520, P30-DK050306, R01-CA171979, P01-CA174439, and R01-CA177423 to ESR. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript. We sincerely apologize to the authors whose important work could not be cited here due to space limitations.

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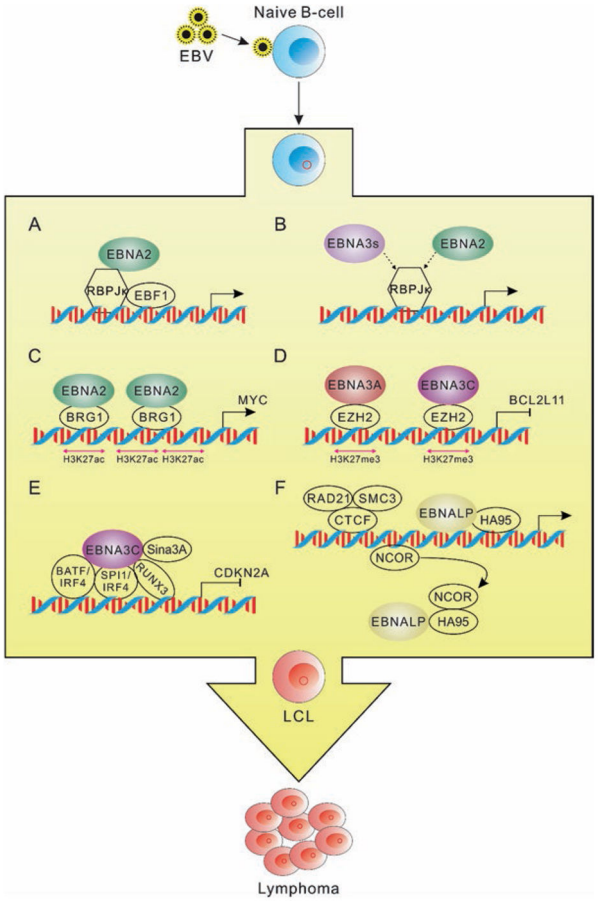

Fig. 5.1.

EBV latent antigen-associated cellular signaling pathways from the current high-throughput sequencing data during EBV-mediated lymphomagenesis. (**a**) EBNA2 regulates target genes expression through the recruitment of transcription factors RBPJκ and EBF1. (**b**) EBNA3s and EBNA2 bind with partially the same RBPJκ genomic sites. The interaction between RBPJκ and EBNA3s or EBNA2 will result in different effects of downstream gene expression, which are also associated with other EBNA-interacting cell transcription factors. (**c**) EBNA2 activates the three clusters of upstream enhancers of *MYC* promoter with increased H3K27Ac and BRG1 binding, and then EBNA2 mediates MYC activation through promoting the interaction of *MYC* promoter and the activated upstream enhancers. (**d**) EBNA3A and EBNA3C repress BCL2L11 expression by inactivating the upstream enhancers of its promoter. The inactivation is associated with increased H3K27me3 and EZH2 binding as well as the inhibition of interactions between BCL2L11 promoter and its enhancers. (**e**) EBNA3C binds to the promoters through BATF/IRF4, SPI1/IRF4, and RUNX and further recruits Sin3A to inhibit CDKN2A expression. (**f**) EBNA-LP regulates the derepression of target genes by removing NCOR repression complex from the promoters with the help of HA95 and further promotes the long-distance enhancer-promoter interaction through CTCF, RAD21, and SMC3 proteins. EBV latent antigens are *highlighted* by colorful patterns, while cellular factors are labeled with colorless patterns

Table 5.1

The transcription factors (TFs) identified in ChIP-seq analysis

Associated TFs[a]	Targets	Cell lines	References
EBNA1	Human genome, EBV latent promoter	Raji	[4]
EBNA2, RBPJG, CTCF, EBF, RELA, H3K9ac, H3K4me1, Pol II, P300	Human genome	GM12878	[51]
EBNA2, EBF1, RBPJk	Human genome, EBV latent promoter	LCL, Mutu III	[52]
EBNA2, H3K27Ac	Human genome	GM12878, Mutu III	[53]
EBNA-LP, *EBNA2*	Human genome	GM12878	[54]
EBNA3C, Sin3A, REST, *EBNA2*, RBPJG, IRF4, BATF, SPI1, RUNX3, p300, Pol II, H3K4me1, H3K4me3, H3K9ac	Human genome	GM12878	[55]
EBNA2, RBPJG, H3K27ac, H3K4me1, BRD4, P300, Pol II, BATF, EBF1, PAX5, SPI1, Sp1, NFAT, STAT5, ETS1, IRF4, CTCF, RAD21, SMC3, YY1; *EBNA3A*, *EBNA3C*, EBNA-LP, RelA, RelB, cRel, p50, p52	Human genome	GM12878	[60]
Notch1, RBPJG, ZNF143	Human genome	GM12878	[109]
EBNA3A, *EBNA3C*, *EBNA2*, RBPJG, BATF, IRF4, SPI1, RUNX3, NF-GB, MEF2A, PAX5, POU2F2, MAX, MYC, POL2, SIN3A, H3K27ac	Human genome	GM12878	[110]
CHD2, CFOS, BRCA, EGR1, PBX3, BCL3, GCN5, p300, TBP, TAF1, CTCF, Pol II, TCF12, EBF1, SP1, PU.1, PAX5, BATF, JUND, SMC3, RAD21, H3K27ac	Human genome, EBV latent promoter	GM12878	[111]
CTCF, RAD21, RPB1	EBV genome	Raji	[112]
Cohesin, RNA Polymerase II			
EBNA3A, *EBNA3B*, *EBNA3C*	Human genome	LCL	[113]

[a] EBV latent antigens are *underlined*