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Review Article

Epstein-Barr Virus-associated lymphoproliferative disorders: experimental and clinical developments

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Abstract: Epstein-Barr Virus (EBV), the first human virus related to oncogenesis, was initially identified in a Burkitt lymphoma cell line in 1964. EBV infects over 90% of the world's population. Most infected people maintain an asymptomatic but persistent EBV infection lifelong. However, in some individuals, EBV infection has been involved in the development of cancer and autoimmune disease. Nowadays, oncogenic potential of EBV has been intensively studied in a wide range of human neoplasms, including Hodgkin's lymphoma (HL), non-Hodgkin's lymphoma (NHL), nasopharyngeal carcinoma (NPC), gastric carcinoma (GC), etc. EBV encodes a series of viral protein and miRNAs, promoting its persistent infection and the transformation of EBV-infected cells. Although the exact role of EBV in the oncogenesis remains to be clarified, novel diagnostic and targeted therapeutic approaches are encouraging for the management of EBV-related malignancies. This review mainly focuses on the experimental and clinical advances of EBV-associated lymphoproliferative disorders.

Keywords: EBV, lymphoproliferative disorders, microRNA, oncogenisis, signaling pathway, targeted therapy

Introduction

Epstein et al. firstly discerned Epstein-Barr Virus (EBV) in a cell line establishes from a Burkitt lymphoma biopsy by electron microscopy in 1964 [1]. EBV was recognized as the first virus to be directly implicated in carcinogenesis. In vitro, EBV can promiscuously infect normal resting B-lymphocytes and almost always transform them into proliferating blasts, exhibiting B-lymphotropic nature [2].

EBV (also called human herpesvirus-4) is an enveloped virus, containing a DNA core surrounded by a nucleocapsid and a tegument. Its linear, double-stranded DNA genome of EBV encodes approximately 100 genes [3]. Although herpes viruses are ubiquitous in nature, humans serve as the only natural host for EBV. EBV-1 and EBV-2 (two subtypes of EBV) are different in geographic distributions and the organization of the genes encoding EBV nuclear antigen (EBNA) [4]. EBV-1 is more prevalent in most populations and is more efficient in transforming infected-B cells [5]. However, EBV-2 is detected frequently in New Guinea, equatorial Africa, and Alaska [6, 7].

Primary infection with EBV typically occurs in childhood and is generally asymptotic. While in adolescence or adulthood, it is associated with a self-limiting infectious mononucleosis syndrome in approximately one third of the cases [8, 9], manifested by fever, pharyngitis, malaise and atypical lymphocytosis [10]. Upon primary infection, most individuals remain a life-long carrier of the virus without serious sequelae [11]. However, a small population will develop neoplasms, including solid tumors and hematologic malignancies [12-14]. This article is to review the current understanding on the role of EBV in the EBV-associated lymphoproliferative disorder from the view of pathogenesis, prognosis, and therapeutic approaches.

EBV infection

EBV is transmitted from host to host by saliva and oral contact in most cases with rare cases of transmission by transfusion [15]. It is gener-

ally hold that EBV infects and replicates within oropharyngeal epithelium in primary infection. This is followed by the infection of circulating B lymphocytes [16]. It is assumed that the peripheral EBV-infected memory B cells can return to Waldeyer's ring, undergo reactivation and produce infectious virus to be shed into saliva. In healthy individuals, both humoral and cellular immune responses are evoked by primary infection of EBV. Antibodies (e.g. IgG, IgM, IgA) against EBV viral capsid antigen or early antigen neutralize the viruses [17, 18], and EBV-specific cytotoxic T lymphocytes (CTLs) destroy most infected cells expressing viral proteins [19-21]. In infectious mononucleosis, almost half of the CD8 (+) cells in the peripheral blood are EBV-specific CTLs [22]. However immune system can't eliminate the virus completely. EBV eventually enters memory B cells and infects nearly 1 in 10,000 to 100,000 memory B cells [23, 24]. In this condition, EBV is non-pathogenic and invisible to the immune system of the host.

In latent infection, the EBV genome is maintained as a multicopy circular episome in the host cell or by integrating the viral DNA into the host genome, the expression of EBV genome is restricted in order to escape the immune surveillance of the host [25, 26]. According to the patterns of expression of EBV genome, latency has been classified into three types (type III latency, type II latency, and type III latency) [27, 28].

EBV infected naïve B cells in the lymphoid tissue of Waldeyer's ring, which express the full spectrum of latent gene products, show type III latency (growth program). The products include 6 EBV nuclear antigens (EBNA1, 2, 3A, 3B, 3C, and LP), 3 latent membrane proteins (LMP1, 2A, and 2B), EBV-encoded RNAs (EBERs) [29, 30]. EBV activates B cells to become proliferating blasts through by the growth program. The naïve infected B cells enter the germinal center (GC) where they proliferate and clonally expand. The germinal center infected cells exhibit type II latency (default program), which characterized by a restricted EBV gene expression pattern (limited to EBNA1, LMP1, LMP 2A and 2B, and EBERs) [31]. Through the process of the germinal center reaction, these infected GC cells differentiate into memory B cells to exit from the cell cycle and enter the peripheral circulation. The EBV-infected memory B cells in periphery expressing only EBERs, so they rarely detected by the immune system. However, some of them that express EBNA-1 protein divide occasionally to maintain the long-term reservoir of EBV, which is referred to type III latency [28, 32].

The exact mechanism that EBV pushes newly infected B cells into long-lived memory B cells is poorly understood when compared with the biology of normal B cell. The Latent protein and genes of EBV may provide part or most of the signals required for the transition from the EBV-infected lymphoblast to a memory B cell, while the rescue signals for the immune-activated B cell blast mainly depend on antigen and antigen-specific helper T cells (Ths) [33, 34]. It is a continuum from a naïve B cell to either a memory cell or plasma cell. Disruption of the normal process by transforming events may cause a clonal expansion and the differentiation blockage of cells resulting in the development of lymphoid malignancies [35].

In the infection cycle, EBV risks the attack by the immune system of host until it finds the excellent shelter in resting memory B cells. In growth program, the lymphoblastoid cells that fail to differentiate out of the cell cycle will be destroyed by the immune response [33]. In addition, the germinal or memory B cells may be directly infected incidentally owing to the high viral load in infectious mononucleosis [36, 37]. These bystander infected B cells, which fail to quit the cell cycle and expand rapidly, will be destroyed by the EBV-specific CTLs [38]. However, the blast cells may develop into lymphomas under aberrant immune surveillance.

Lauri, L. et al. found that the promoter for immediate-early BZLF1 gene (the gene that begins viral replication) becomes active only after memory cells differentiate into plasma cells [39]. The differentiation of B cells into plasma cells in tonsil may provide the signal for the lytic cycle. It is suggested that the EBV-infected peripheral B cells constitute a functional reservoir which can differentiate into plasma cells, complete the viral cycle and secrete viral particles [40].

EBV-associated lymphoproliferative disorders

The initial link between EBV and lymphoproliferative disorders begins with the study of Burkitt lymphoma [1]. The capacity of EBV to

immortalize B-lymphocytes in vitro and turn them into lymphoblastoid cell lines was soon demonstrated. Subsequently, EBV was proven to be the causative agent in most infectious mononucleosis [41]. Now, EBV infection has been an area of active research in Hodgkin's lymphoma (HL), non-Hodgkin's lymphoma (NHL), and immunodeficiency-related lymphoproliferative disorders. The classification system of EBV-associated lymphoproliferative disorders is comprehensive and ever-changing, containing not only clinical characteristics but also the features of morphology, immunology, cytogenetics, and molecular genetics [27].

Hodgkin's lymphoma (HL)

Hodgkin's lymphoma is a distinct disorder accounting for 30% of lymphoid malignancies worldwide. It is marked by the presence of neoplastic cells called the Reed-Sternberg (HRS) in the inflammatory milieu [42]. The following evidence implies the association between EBV and HL. In 1971, Levine et al. reported the elevated antibodies titers to EBV antigens in Hodgkin lymphoma patients [43]. Moreover, it was also observed that individuals with a past history of infectious mononucleosis are more susceptible to HL [44]. In 1987, EBV DNA was detected in lymphoid tissues of Hodgkin's lymphoma with southern blot hybridization [45]. Subsequently, the presence of EBV DNA in HRS cells was confirmed by situ hybridization and single-cell PCR [46, 47].

Different subtypes of HL vary greatly in the EBV presence. EBV positivity in lymphoma tissue is detected in ~70% of mixed cellularity (MC) subtype, > 95% of lymphocyte-depleted (LD) subtype, and 10-40% of nodular sclerosis (NS) subtype; the lymphocyte-predominant (LP) subtype is almost always EBV negative [48]. The incidence of EBV in HL also has geographic variations. Percentage of EBV incidence observed in HL patients of developed countries is 30%~50%, whereas the percentage is nearly 100% in children of developing countries [49-53]. Moreover, the association of EBV with Hodgkin's lymphoma seems to be stronger in pediatric and older cases compared with young adults [54-56], which may to be partly related to the less developed and senescent immune system respectively.

It is still controversial with regard to the origin of HL. Although T-cell origin is postulated in rare cases of HL, hypermutation of immunoglobulin gene in HRS cells is highly consistent with GC B cells. Moreover, type II latency of EBV in HL supports the GC B origin of HL. Molecular analysis demonstrates that HRS cells often carry nonsense or crippling mutations in the variable region of immunoglobulin genes [57]. Unexpectedly, some unknown survival signals rescued such cells which should be eliminated by the programmed cell death (apoptosis) in germinal center under normal circumstances [58].

HRS cells exhibit type II latency (expressing LMP1, LMP2A and 2B, EBNA1, and EBERs) provides some clues for the oncogenic potential of EBV in the transforming events of HL which remains poorly understood. LMP-1 has been postulated to act as a constitutively active CD40 receptor by self-aggregation and oligomerization, resembling the cellular growth signal that normally results from the binding of CD40 ligand [59, 60]. Several oncogenic signaling pathways have been implicated in the function of LMP-1, such as nuclear factor-κB (NF-κB), C-Jun NH2-terminal kinase (C-Junk), p38 mitogen-activated protein kinase (P38MAPK), and Janus kinase/signal transducers and activators of transcription (JAK/STAT) [61-64]. LMP-1 also protects the EBV-infected cells from apoptosis by increasing the expression of Bcl-2 and A20 [65, 66]. LMP2A has been reported to mimic the presence of BCR in transgenic mice [67]. What's more, EBV BCRF1 protein exhibits homology to human IL-10, which is essential for the suppression of host immune system [68]. However, the exact role of EBV in the development of HL remains poorly understood.

B-cell non-Hodgkin's lymphoma

Owing to the preferential infection of B-lymphocytes, EBV is predominantly implicated in hematologic malignancies of B-cell type. The EBV-associated B-cell non-Hodgkin's lymphomas reviewed below include Burkitt lymphoma (BL), EBV-positive diffused large B cell lymphoma (DLBCL) and so on.

Burkitt lymphoma (BL) is a particularly aggressive B-cell lymphoma with enhanced cell proliferation and rapid tumor progression [69]. According to distinct clinical and epidemiologic features, BL is categorized into three variants: endemic BL (eBL), sporadic BL (sBL), and HIV associated BL. EBV has been detected in >

90% cases of eBL (affecting children in equatorial Africa and New Guinea), but only 15%-20% in sBL (affecting children and young adults worldwide) and 30%-40% in the HIV-related BLs [70-72]. Almost all the three subtypes exhibit c-myc translocation, such as t(8;14)(q24;q32) and its variants [71, 73], which has become a hallmark of BL [74]. The contribution of EBV and c-myc translocation to BL is far more complicated.

Most EBV positive BL cases exhibit a restrictive pattern of EBV-genome (EBERs and EBNA-1), which is referred to latency I as seen in memory B cells of healthy carrier [32, 71]. However, it is generally hold that BL is a tumor of GC B cell origin, considering that the phenotype of the BL cells is highly consistent with the GC cells [75, 76]. Takada, K. et al. believed that EBV contributed to the malignant phenotype of Akata BL cell line [76]. The experimental formation of aggressive lymphomas in cotton-top marmosets and owl monkeys also implicated the oncogenic potential of EBV [1]. Nevertheless, EBV was regarded as a passenger for BL rather than the initiating factor by some doubters, considering the variable EBV association in the 3 subtypes.

In addition, EBV is necessary yet not sufficient to cause eBL. With regard to the co-infection of EBV and Pf-malaria in eBL etiology, there are two prevailing theories. One assumes that B-cell expansion and EBV reactivation induced by Pf-malaria increases the number of latently infected B-cells and the possibility of c-myc translocation [77-81]. The other theory argues that EBV-specific T-cell immunity is impaired during Pf-malaria co-infection, leading to the escape of EBV-infected B cells (including those with cmy-translocation) [82-85]. The exact oncogenic mechanism behind the co-infection remains to be elucidated.

Diffuse large B-cell lymphoma (DLBCL) is the most common lymphoid neoplasm worldwide, accounting for 30% to 40% of all non-Hodgkin's lymphoma (NHL) [86]. It has been revealed that DLBCL is a group of aggressive lymphomas with great heterogeneity in morphologic, molecular genetic, and clinical features [87]. Germinal center B cell-like (GCB) and activated B cell-like (ABC) are the two subsets of DLBCL according to the cell-of origin model. EBV is usually present in post-transplant DLBCL and HIV-associated DLBCL in the setting of immune impairment. Lymphomatoid granulomatosis (LYG), plasmablastic lymphoma (PBL), primary effusion lymphoma (PEL) and DLBCL associated with chronic inflammation, are frequently seen in immunosuppressive patients and exhibit type III latency of EBV. However, in immunocompetent hosts, EBV-infection is only associated with DLBCL in about 10% of cases [88]. Depending on different immune status of EBV-positive DLBCL cases, EBV infection exhibits type II or III latency. The number of EBER positivity may range from 10% to almost all tumor cells of DLBCL. Increasing evidence suggests that DLBCL occurring in perhaps immunosenescence of aging are more frequently associated with EBV [86, 88]. Immunosenescence may rely on multiple factors, such as thymic atrophy, decrease of B-cell diversity, accumulation of anergic memory cells, reduction of T cells cause by persistent infection.

In the 2008 WHO classification, EBV-positive DLBCL of the elderly is defined as an EBV-positive monoclonal large B-cell lymphoproliferative disorder arising in immunocompetent patients > 50 years [89]. The incidence of EBV-positive DLBCL of the elderly among DLBCL in Asian or Latin American countries ranges from 8 to 15% [75, 90-92], whereas it is only < 5% in Western populations [93, 94].

There are no uniform cutoffs for EBER positivity used by investigators worldwide [90, 95, 96]. Most EBV-positive DLBCL of the elderly patients have an activated B-cell (ABC) immunophenotype with predominant activation of NF-κB pathway [97]. Increasing studies have observed that this provisional entity has an aggressive clinical course manifested by poorer response to chemotherapy and worse outcome compared with the age-matched DLBCL without EBV infection, independent of the International prognostic Index [75, 90, 98].

EBV-positive DLBCL have also been reported in individuals younger than 50 years old without apparent immunodeficiency [90, 91, 94, 99]. What's more, Melina Cohen et al. reported the association of EBV in pediatric DLBCL patients of Argentina [100]. These reports suggest that EBV-positive DLBCL is an entity that is not restricted to patients who are older than 50 years of age. However, many doubters believe that these younger patients should be excluded

because they may have an underlying or undetected immunodeficiency.

EBV positivity was associated with a worse prognosis of DLBCL in many reports [75, 90, 91]. No uniformed strategies have been achieved for the EBV-positive DLBCL besides the standard therapy for DLBCL (rituximab-containing regimens). More studies are needed to evaluate the effect of rituximab on EBV-positive DLBCL. The novel approaches, such as EBV-specific adoptive immunotherapy, application of novel antiviral dugs, oncogenic-pathway targeted and miRNA-targeted agents, may be promising in the future [101-103].

T/NK-cell non-Hodgkin's lymphoma

EBV can infect peripheral blood T cells as well as NK cell in a few patients with infectious mononucleosis [104]. Since the EBV association with T-cell proliferation was first described in patient with chronic EBV infections [105], several T/NK-cell non-Hodgkin's lymphomas have been linked to EBV, although the role of EBV in these disorders is largely unknown.

Angioimmunoblastic T-cell lymphoma (AILT) is one of the most common subtypes of peripheral T-cell lymphoma (PTCL), which is manifested by generalized lymphadenopathy, hepatosplenomegaly, anaemia and hyper gammaglobulinaemia [106]. The lymph node histology shows the partial effacement of the lymph node architecture by a polymorphic infiltrate of lymphocyte, transformed lymphoid blasts, vascular proliferation and follicular dendric cells (FDCs) [106]. EBV genome has been detected in > 95% of AITL lymph nodes by southern blot and PCR [107, 108]. Most notably EBV presence is detected virtually in B cells, whereas rarely seen in T cells of AILT [109], suggesting that EBV infection may be secondary to oncogenesis or that the EBV genome has been lost from the malignant cell [25].

There is an assumption that an underlying immunodeficiency with reduced cytotoxic activity contributes to the outgrowth of EBV-infected cells. The function studies of the T cells recovered from lymph nodes and peripheral blood of AITL patients indicated an underlying immunodeficiency. This was manifested by a reduction of the absolute number of circulating T cells, inversion of the CD4/CD8 ratio, high percentages of activated T cells (CD8+/HLA-DR+), defective T-cell response in vitro to the phytohaemagglutinin (PHA) mitogen and minimal enhanced in vitro suppressor functions [110]. AILT-associated immunodeficiency caused by chemotherapy may also facilitate the EBV-infected B cells to proliferate and transform [111]. However the cytotoxic phenotype of the tumor cells, characterized by T cell intracellular antigen 1 (TIA-1) and granzyme B, provides a hypothesis that EBV-association T cell lymphomas may derived from the proliferating of cytotoxic T cells trying to kill the EBV-infected cells [31].

The latency pattern for EBV in AITL has not been determined although some have assumed a restricted latency II program evidenced by the expression of LMP1 and the EBERs of B cells in some AITL cases [71]. The EBV-positive B cells may play a role in maintaining the malignant T-cell process [112]. In Yang's report, EBERs increased the expression of IL-9 and consequently promoted T-cell proliferation and transformation [113].

Extranodal nasal NK/T-cell lymphoma is a rare tumor with a distinctive ethnic and geographical distribution, which accounts for 7% to 10% of all NHL cases in Asia and Latin America, but only 1% of that in Caucasians [114-116]. The nasal region is the most frequent site of involvement but the tumor may also invade other extranodal sites such as skin, kidney, gastrointestinal tract, and the orbit [117, 118]. The genotypic and phenotypic features of nasal NK/T-cell lymphoma include the expression of the NK cell marker CD56 and an absence of T-cell antigens and T-cell receptor gene rearrangement [119]. This tumor is almost always associated with EBV which may be directly involved in lymphomagenesis [120, 121]. However, the role of EBV in nasal NK/T-cell lymphoma is yet to be clearly defined.

The expression of the latent EBV proteins LMP1, EBNA1, and EBER has been detected in the lymphoma cells, which pertains to type II latency of EBV [122]. LMP1 is supposed to increase the sensitivity of the infected NK cell to the growth-promoting effects IL-2 [123]. The high level of circulating plasma EBV DNA has been correlated with high tumor load, extensive disease, poorer response to treatment, and inferior survival [124-126]. EBV-targeted thera-

py may be promising considering its constant presence in nasal NK/T-cell lymphoma that remains incurable in spite of the multi-agent chemotherapy and radiotherapy.

Post-transplant lymphoproliferative disorder (PTLD)

Post-transplant lymphoproliferative disorder (PTLD) is a heterogeneous collection of lymphatic and plasmacytic proliferations affecting individuals with therapeutic immunosuppression after organ transplants [127]. PTLDs contain polyclonal early lesion, polymorphic PTLD, monomorphic B-cell PTLD, monomorphic T-cell PTLD, and classical Hodgkin lymphoma-type PTLD [128]. The incidence of PTLDs may rely on multiple factors, such as the transplant types, the age of patients, the EBV status of the transplant recipient and donor, intensity of immunosuppression, concurrent cytomegalovirus [129, 130].

Although the real pathogenic process of PTLD remains unclear. Notably, EBV has been linked to PTLD with a presence of 70%-100% in PTLD cases. EBV positivity is nearly 100% in early PTLD (within a year after transplantation) and PTLD-related Hodgkin lymphoma, and about 34-80% in late PTLD (usually 5 years post transplantation) [25, 131]. Most EBV positive B cells in PTLD exhibit type III latency with a wide expression of the latent EBV-encoded proteins, indicting an important role of EBV for the development of PTLD [129]. The mechanism by which EBV contributed to oncogenesis of PTLD is presumed to be similar with that in HL considering half of PTLD cases are derived from GC B cells [132, 133]. LMP1 and LMP2A may resemble the survival signaling normally produced by CD40 and activated BCR to prevent the apoptosis of infected GC without functional BCR, leading to the proliferation of neoplastic cells [134, 135]. In addition, therapeutic immunosuppression may also facilitate the primary infection or reactivation of EBV followed by the expansion of B cell with a selective growth advantage.

PTLD prophylaxis, including prevention and treatment of EBV reactivation, have shown efficacy to reduce the incidence of PTLD in several observations [136, 137]. Although many therapeutic strategies have been reported, such as EBV-specific targeted approaches, appropriate immunosuppression reduction (IR) and combination of rituximab with chemotherapy [138, 139]. More experimental and clinical studies are in a dire need.

HIV-related lymphoproliferative disorders

HIV-associated lymphoproliferative disorders (LPDs) represent a heterogeneous group of diseases arising in the setting of HIV-associated immunosuppression, most of which are highly aggressive and of a B-cell origin [140]. One recent epidemiologic study found that NHL comprises 53% of all AIDS defining cancers [141]. HIV-related lymphomas contain (1) subtypes that can also occur in general population (e.g. such as HL, BL, DLBCL and PTCL) and (2) subtypes occurring almost exclusively in the presence of HIV infection, such as primary effusion lymphoma (PEL), plasmablastic lymphoma (PBL) of the oral cavity. There are many supposed risk factors for HIV-related lymphomas, such as immunosuppression, cytokine deregulation, chronic antigen stimulation, opportunistic infections with oncogenic virus such as EBV and HHV8 [140, 142].

It is reported that EBV has been detected in up to 60% of all HIV-related lymphomas, and that including nearly 100% of primary CNS lymphomas, 80% of DLBCL with immunoblastic features, 30% to 50% of BLs, 60% of PBLs, 70% of PELs, and nearly 100% of HLs arising in the setting of HIV infection [143-145]. The latent types of EBV infection in HIV-related lymphomas generally depend on the histologic subtype of lymphoma. We will focus on the subtypes arising more specifically in HIV-positive patients.

Primary central nervous system lymphoma (PCNSL) is virtually a subtype of DLBCL that is much more common in HIV-infected individuals [145]. PCNSL arises in 0.5% of patients with AIDS, accounting for 20% to 25% of all HIV-related lymphomas [140, 146, 147]. EBV can be detected almost in all cases of AIDS-related central nervous system lymphomas [30], which exhibit type III latency. A few studies have reported the presence of EBV in the cerebrospinal fluid (CSF) of HIV-positive patients with a CNS lesion infers a diagnosis of lymphoma [148, 149].

Primary effusion lymphoma is a rare tumor affecting body cavities without a detectable

tumor mass [150]. The immunoglobulin gene rearrangements and somatic hypermutations of the neoplasm cells support the post-GC B-cell origin [151, 152]. Dual infection with HHV-8 (also called Kaposi's sarcoma associated herpes virus) and EBV (also called HHV-4) has been detected in up to 70% of the PEL cases [143, 153]. The expression of EBV latent encoded proteins in PELs is restricted to EBNA1, LMP1, LMP2A, and EBERs, which referred to type II latency [143, 154]. The prevailing assumption is that EBV may act as a cofactor in the initiating events (because it can immortalize and transform B cells in vitro) whereas HHV-8 may be the driving force for the tumor [151, 155]. The real role of EBV in PEL remains indeterminate.

Plasmablastic lymphoma (PBL) is a rare tumor predominantly seen in the in the oral cavity of HIV-positive patients [156-158]. EBV has been detected in approximately 60% of the PBL cases regardless of the HIV status, whereas EBV genome expression is restricted to the EBERs [144, 145]. The potential role for EBV in the pathogenesis of PBL remains a mystery to be unrevealed.

Therapeutic strategies

Although increasing evidence has demonstrated the potential role of EBV in EBV-associated lymphoproliferative disorders (LPDs), no unified targeted therapeutic strategies have been established. At present, novel therapeutic approaches with promising results have been widely investigated.

Antivirals in clinical use are mainly broad-spectrum anti-herpes virus and anticytomegalovirus agents with variable anti-EBV effect, such as acyclovir, ganciclovir, and valaciclovir. However EBV is not in lytic phase and viral thymidine kinase enzyme (required for the antiviral reaction) is not expressed in most EBV-associated lymphoid disorders, resulting in the declined anti-EBV activity. The combination of induction of EBV lytic phase with subsequent exposure to anti-herpes virus drugs has shed new light for a better therapy. The proposed lytic phase inducers include DNA methylase transferase inhibitors, histone deacetylase inhibitors, proteasome inhibitors, B-cell receptor-blocking antibodies, chemotherapeutic drugs, and cellular miRNAs [101, 102, 159, 160]. Combinations with optimal antiviral and anti-tumor effects remain to be determined.

Adoptive immunotherapy has been reported by Walter et al. in the control of cytomegalovirus of bone marrow transplant recipients [161]. Similar strategy has been intensively studied in the management of EBV-associated LPDs. EBV-specific CTLs recovered from a donor can be infused directly into the patient or expanded in vitro and then infused to reestablish immunocompetence, which is a time-consuming, costly and labor-intensive process [162]. EBV-specific CTLs can recognize and eliminate the EBV-infected tumor cells, which seems to be feasible for the EBV-associated LPDs expressing more latent proteins. It has been reported that EBV-specific CTLs was administrated in the management of EBV-associated LPDs; such as EBV-associated PTLD, EBV-associated HL and EBV-positive DLBCL [163, 164]. However, the clinical experience of the EBV-specific adoptive immunotherapy remains deficient and the therapy response remain undetermined. What's more, there are many potential risks for patients infused with the EBV-specific CTLs, such as the graft-versus-host disease (GVHD) and tumor resistance caused by the mutations of EBV.

Monoclonal antibodies have provided promising outcome in the targeted therapy of EBV-associated LPDs [165, 166], such as rituximab (anti-CD20 monoclonal antibody) which has been used in a variety of CD20-expressing lymphomas [167-169]. A response rate of 69% (mostly complete responses) has been reported in a group of transplant recipients [170]. More data is needed on the use of rituximab-based regimens. Brentuximab Vedotin, an antibody-drug conjugate (ADC) directed to the protein CD30, is under further clinical trial as well [171, 172]. More monoclonal antibodies specified for the tumor cells are anticipated.

Approaches targeting oncogenic pathways have been intensively studied based on the aberrant oncogenic signaling detected in EBV-associated LPDs. EBV latent proteins can also interact with or exhibit homology to many anti-apoptotic molecules, cytokines, and signal transducers, promoting EBV infection, immortalization, and transformation [25]. Bortezomib (a proteasome inhibitor) has been found to induce apoptosis of EBV lymphoblastoid cell lines by inhibiting NF-κB pathway [173]. Some

experiments show that inhibition of the LMP1/LMP2A-activated PI3K/Akt signaling can also reduce the activity of NF-κB pathway [174]. In addition, EBV-associated LPDs have been lined to a number of EBV miRNAs which can modulate oncogenic or tumor suppressor pathways (e.g. p53, c-MYC, RAS) [175], which provide rationale for the miRNA-targeted therapeutic approaches. EBV was the first virus where miRNAs were detected. It has been reported that EBV-infected cells can shed viral miRNAs to non-infected cells by exosomes. There are two main clusters including BART (mRNAs BamHI-A rightward transcript) and BHRF1 mRNAs (BamH1 fragment H rightward open reading frame 1) [175, 176], many of which have been involved in lymphomagenesis by interact with viral and cellular genes. For example, EBV-miR-BART5 prevents apoptosis of transformed cells by degrading p53-up-regulated modulator of apoptosis (PUMA) [177]. EBV-miR-BART9 and BART17-5p can down-regulate the expression of BCL6, eventually activating NF-κB pathway [178]. EBV-miR-BHRF1 is crucial for efficient B-cell transformation [179, 180]. EBV miRNAs may become valuable biomarkers and therapeutic targets in the future.

Conclusion

EBV has been implicated in a wide range of human tumors. The current understanding has revealed the role of EBV in the initiation, acceleration or maintenance of EBV-associated lymphoproliferative disorders. The mechanisms, by which EBV maintains its latent infection and contributes to the lymphoid malignancies, remain to be elucidated. Although the therapy for EBV-associated lymphoproliferative disorders is largely nascent, considerable novel approaches have been reported to be promising. These approaches include application of new antivirals, adoptive immunotherapy, therapy targeting oncogenic miRNA or signaling pathway. Further experimental and clinical data is needed to improve therapeutic strategies for EBV-associated lymphoproliferative disorders.

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Disclosure of conflict of interest

None.

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