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Review

Advancing therapeutic strategies for Epstein-Barr virus-associated malignancies through lytic reactivation

Haiqi Tan [a,b,1], Yibing Gong [a,b,1], Yi Liu [a,b], Jingyi Long [a,b], Qingshuang Luo [a,b], Oluwasijibomi Damola Faleti [a,b,c], Xiaoming Lyu [a,b,*]

[a] Department of Laboratory Medicine, The Third Affiliated Hospital, Southern Medical University, Guangzhou 510630, China
[b] The Third School of Clinical Medicine, Southern Medical University, Guangzhou 510630, China
[c] Department of Applied Biology and Chemical Technology, The Hong Kong Polytechnic University, 999000, Hong Kong Special Administrative Region of China

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ABSTRACT

Epstein-Barr virus (EBV) is a widespread human herpes virus associated with lymphomas and epithelial cell cancers. It establishes two separate infection phases, latent and lytic, in the host. Upon infection of a new host cell, the virus activates several pathways, to induce the expression of lytic EBV antigens and the production of infectious virus particles. Although the carcinogenic role of latent EBV infection has been established, recent research suggests that lytic reactivation also plays a significant role in carcinogenesis. In this review, we summarize the mechanism of EBV reactivation and recent findings about the role of viral lytic antigens in tumor formation. In addition, we discuss the treatment of EBV-associated tumors with lytic activators and the targets that may be therapeutically effective in the future.

1. Introduction

Epstein-Barr virus (EBV) is a herpesvirus subfamily member with a diameter of about 150–170 nm [1]. EBV consists of three basic components: the outer lipid bilayer envelope with external membrane glycoprotein, the middle pleomorphic tegument compartment, and the inner icosahedral nucleocapsid, which wraps a linear double-stranded DNA (dsDNA) of 172 kilobases in length [2]. EBV infection is widespread, with about 95 % of the world's population reported to be EBV-positive [3]. The virus infects a wide range of human cells. It is, however, lymphotropic [4], which makes B cells its prime target host for latent infection. Aside from B cells, EBV also infects oropharyngeal epithelial cells, which play a crucial role in virus transmission to new hosts [5]. EBV is the first oncovirus discovered [6] and it is implicated in at least 265,000 carcinoma cases and 164,000 cancer-related death per year. Malignancies associated with EBV include Nasopharyngeal carcinoma (NPC) [7], Burkitt's lymphoma (BL) [8]; some subsets of Hodgkin's disease (HD) [9]; nasal NK/T lymphoma (NKTL) [10]; post-transplant lymphoma (PTLD) [10]; plasmacytoid lymphoma [11]; extranodal natural killer (NK)/T-cell lymphoma, nasal type (ENKL) [12]; diffuse large B-cell lymphoma (DLBCL); and gastric cancer (GC) [13]. Consequently, EBV is regarded as a class I carcinogen by the World Health Organization (WHO) [14].

In the host, EBV exhibits a biphasic infection consisting of latent infection and lytic infection. During latent infection, EBV's genome replicates simultaneously with the host genome as an episome in the nucleus. This phase can help the virus genome persists for a long time. The property has led to extensive research on its role in tumorigenesis. And the result revealed that latent EBV infection contributes to oncogenesis in many ways which include maintaining latent EBV infection, enhancing genome instability [15] , avoiding immune destruction [16–18] , resisting cell death [19,20], sustaining proliferative signaling and enabling replicative immortality [21,22], activating metastasis, angiogenesis [23], and tumor-promoting inflammation [24]. During lytic infection, the lytic genes of EBV are amplified over 100-fold and expressed coordinately. This phase could help viruses produce infectious viral particles. However, the role of lytic infection in tumorigenesis has rarely been studied for the reason that it may lead to cell death. The role of lytic infection in tumorigenesis is underestimated. Recent evidence has emerged to show that it can also contribute to inflammation and

* Correspondence to: Department of Laboratory Medicine, The Third School of Clinical Medicine and The Third Affiliated Hospital, Southern Medical University, Guangzhou 510630, China.
E-mail address: xiaomlyu@smu.edu.cn (X. Lyu).
[1] These authors contributed equally to this work.

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angiogenesis through the expression of some lytic proteins and the secretion of some associated cytokines and growth factors. This reminds us that lytic infection with EBV can likewise promote tumors in many ways.

In this review, we briefly describe the EBV life cycle, the factors that promote lytic infection, and the relationship between lytic infection and tumorigenesis. In addition, we further provide insight into treatment strategies targeting these pathways.

1.1. EBV life cycle

EBV is mainly transmitted via saliva. It enters the oropharyngeal epithelial cells by binding to integrins αvβ5, αvβ6, αvβ8 and Ephrin receptor A2 receptors of epithelial cells [25,26]. Besides, it also pass through the discontinuous epithelial lining of the oropharynx and contact with the underlying B lymphocytes. After interaction between its surface glycoprotein (gp350/gp220) and CD21 or CD35 protein on B cells [25,27], gH/gL-gp42 binds to the receptor human leukocyte antigen (HLA) class II which triggers gB to mediate the merging of the two cells [28,29].

The initial EBV infection of primary B cells immediately triggers a temporary abortive lytic cycle that is characterized by the expression of some lytic genes, such as BZLF1 BRLF1,BGLF4,and BFRF3 [5,30]. After that, the virus moves from a transient lytic state to latent phase III (the growth program). The virus expresses associated latent proteins during this stage, which comprise three latent membrane proteins (LMPs 1, 2A, and 2B) and six EBV nuclear antigens (EBNAs 1, 2, 3A, 3B, 3C, and EBNA-LP). In addition, viral non-coding RNAs (EBER1, EBER2, miRNAs-BHRF1 and miRNAs-BARTs) are also abundant during EBV latent stage[31]. The increased expression of viral antigens triggers a strong immune T-cell response[32], leading to the elimination of most cells in this phase. Despite this, a small number of cells survive the immune elimination and continue to be recruited to the germinal centers [33]. There, they first differentiate into centroblasts and then centrocytes [34]. Cells under latent phase II will eventually enter the circulating bloodstream to transform into resting memory B cells, which is the primary site of EBV lifelong persistence. During the resting stage, the virus generally shuts down the expression of all latent genes and enters latent phase 0 (latency program) [35]. However, EBV occasionally expresses immunogenic EBNA1 proteins in small amounts to ensure replication and persistence of the viral genome during latent phase I [16,36]. After stimulation, infected memory B cells will be activated and recruited to the germinal center, where they differentiate into plasma cells and reactivate EBV to commence the lytic cycle [37]. There are three main lytic stages in the lytic program. including immediate early (IE), early(E), and late (L) phases [4]. During the lytic phase, the virus mainly undergoes DNA replication and synthesis of the viral capsid structure. After successful assembly and wrapping, the newly synthesized virion is eventually released from the infected cell by exocytosis or cell lysis. The released virion infects a new target cell or is released directly into the saliva to infect the next host.

1.2. Lytic cycle

Over the last decade, the carcinogenic potential of EBV latency has been deeply examined. The role of the lytic EBV infection on tumorigenesis appears to be underestimated for the reason that it may lead to cell death [38]. however, the lytic EBV infection could promote oncogenesis by producing infectious viral particles and some binding effector proteins. There is a significant knowledge gap in our understanding of the lytic phase's role in carcinogenesis. To fully understand this tumorigenic impact, we describe the life cycle of EBV and focus on its lytic phase in Fig. 1 before further elaboration.

(1) EBV infects primary B cells. (2) EBV genome is injected into the nucleus through the nuclear pores. (3) The linear genome is circularized and chromatized and remains in the nucleus of the host cell as an episome. (4) Most infected cells undergo a brief abortive lytic phase and express some early lytic genes without producing viral particles. (5) After that, cells enter the latent phase and express latency-associated genes. (6) Stimulation by certain factors lead to the reactivation of EBV. (7) And then, EBV goes through the immediate-early (IE) phase in which Rta and Zta proteins are activated to prompt EBV to enter the early (E) phase. (8) During the early (E) phase, seven EBV encoding proteins, which are important to lytic replication, bind orilyt (origin of lytic replication) to initiating replication: the oriLyt binding protein (BZLF1), primase (BSLF1), the DNA polymerase (BALF5), single-stranded DNA binding protein (BALF2), DNA polymerase processivity factor (BMRF1), helicase (BBLF4), the helicase-

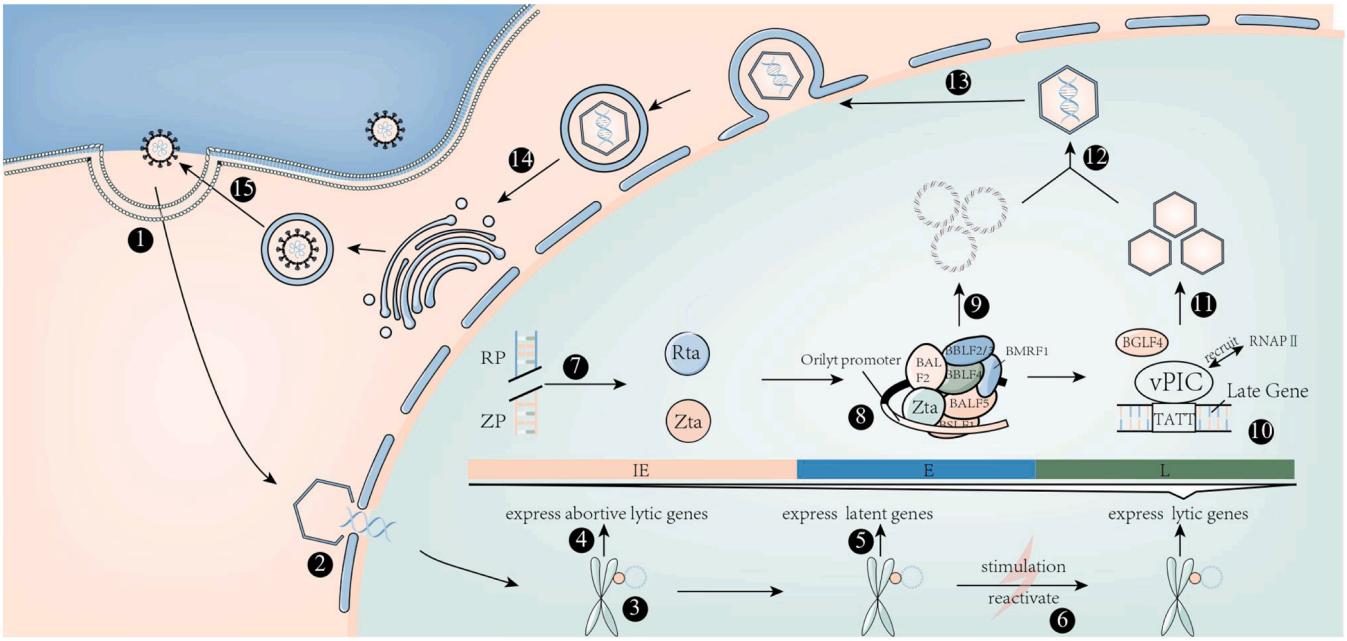

Fig. 1. lytic cycle of EBV.

primase complex (BBLF2/3). (9) After massive replication of the viral genome, (10) Cells then enter the Late (L) phase where vPIC and BGLF4 aid in the expression of late genes. vPIC (viral pre-initiation complex) consists of six late gene regulators. It can bind to the TATT box, the initiation sequence of late genes, to activate late genes expression, and it can also recruit the RNA polymerase II (RNAPII) to late promoters. In addition, the viral protein kinase BGLF4 also plays a key role in this process. (11) Late genes encode structural proteins, such as capsid proteins which are required for the assembly of virions. (12) After assembly of the replicated viral genes with previously synthesized procapsid, mature nucleocapsids are generated. (13) Initial envelopment at the nuclear membrane. (14) secondary envelopment in the viral assembly compartment. (15) Mature viral particles in vesicles are transported to the cell membrane or released after cellular cytokinesis.

The EBV genome is amplified by around a thousand times during the lytic infection phase [3]. The lytic phase products mediate viral genome amplification, structural protein synthesis, viral capsid formation, and the production of new virions in saliva [39,40].

During the immediate early phase, the promoters of the IE proteins BZLF1 (also called Zta, Z, ZEBRA) and BRLF1 (also called Rta) are activated and expressed upon induction of stimuli that activate B cells. These transcriptional activators promote viral early gene transcription and start viral DNA replication once these IE genes reach a particular threshold of expression [41]. Meanwhile, early lytic proteins and DNA replication cause late lytic proteins to be expressed, such as glycoprotein B (gB and gp350), major capsid protein (MCP), major tegument protein (B, NRF1) and viral capsid antigen (VCA), which ultimately result in the creation of infectious viral particles [42]. After that, these particles will complete their assembly in the nucleus and are delivered to the cytoplasm via the nuclear membrane [40].

There is growing evidence that viral lytic proteins regulate host cell cycling, proliferation, apoptosis, and immunological recognition, which can enhance oncogenesis in EBV-positive cancer cells. Thus, searching for new therapeutic targets for EBV-associated malignancies from the lytic perspective is of great importance.

2. Tumors associated with EBV infection

As mentioned above, EBV infection is a key oncogenic driver in the development of EBV-associated cancers. EBV has a dual B cell-epithelial cell tropism and infects other types of human cells, including T cells, NK cells and mesenchymal cells[28].

There is a strong association between EBV infection and lymphoproliferative disorders and malignant lymphomas including BL, PTLD, DLBCL, and HL etc[43]. Dysregulation of c-myc(v-myc avian myelocytomatosis viral oncogene homolog) gene expression is a major determinant of the highly proliferative phenotype of BL[44]. There is substantial evidence that latency I encoding gene increases a c-MYC-induced sensitivity to apoptosis, thereby reversing the pro-senescence and pro-apoptotic signal that accompanies elevated c-myc expression[45,46]. In contrast, classical Hodgkin lymphoma (cHL) consistently exhibits latent phase II infection, in which rare malignant Hodgkin and Reed-Sternberg (HRS) cells are surrounded by an extensive but ineffective inflammatory/immune cell infiltrate. The EBV-encoded proteins expressed in virally infected HRS cells can promote the growth and survival of cHL-derived cell lines by inducing dysregulation of signaling pathways and promoting chemokine and cytokine expression to recruit TME cells [47–50].

Epithelial cells are a natural reservoir for EBV amplification. Many studies have shown that genome-wide hypermethylation is characteristic of EBV-infected epithelial carcinomas[51], and common epithelial carcinomas include NPC, EBVaGC, lymphoepithelioma-like carcinoma (LELC), and Primary pulmonary lymphoepithelioma-like carcinoma (PLELC)[43]. Epithelial carcinoma infection occurs mainly during latency II, a period in which potential genes induce genomic instability along with increased resistance to host immune response and death, ultimately manifesting as a hypermethylated phenotype and cancerous features of epithelial malignancies [13,52].

Associated T/NK tumors are ENKTL, PTCL, STLC, ANKL, and AITL. Studies have shown that T/NK cells are not found in immunodeficient clinical individuals, which may imply that T/NK cell lineage proliferation is not dependent on impaired EBV-specific surveillance but rather is evaded by immune surveil-lance of infected NK/T cells [53]. Infected NK cells can trigger the recruitment and activation of additional cytokines, to stimulate cell growth through autocrine or paracrine production [54]. Mesenchymal cells are seen in smooth muscle sarcomas, which we do not describe too much here. The above highlights that EBV infection includes periods of latent and lytic reactivation driving the progression of cells progression and malignant phenotypes, suggesting an interplay of dual cycles in the mechanism of malignancy.

3. Lytic inducers

Epigenetic modifications play a central role in the regulation of BZLF1 and BRLF1 induction, which are the primary triggers for EBV reactivation. Many factors can also induce the reactivation of EBV by activating signaling pathways such as PKC, PI3K and P38 MAPK. They can broadly be categorized categorize as chemical inducers, e.g., phorbol esters, histone deacetylase (HDAC) inhibitors, DNA methylase inhibitors, or biological stimulants (e.g., transforming growth factor β (TGF-β)). Each factor employs a unique way to induce EBV reactivation.

3.1. Synergistic activation of EBV lytic promoters by Zta and Rta

The expression of two immediate-early (IE) genes of EBV, BZLF1, and BRLF1, encodes the early proteins Zta and Rta, which are essential for the lytic phase of EBV infection. In most EBV-positive cell lines, synthesis of the Zta protein is sufficient to trigger the transformation of the virus [55,56]. Zta activates EBV lytic gene promoters by binding to a set of critical ZRE sites within oriLyt, the site of lytic replication, thereby inducing the cascade expression of more than 50 viral genes [57]. The direct interaction between Zta and core viral replication proteins may facilitate the formation of replication complexes [55]. Like Zta, Rta is a transcriptional activator and sequence-specific DNA-binding protein. In some EBV-positive cell lines, Rta can also convert EBV latently infected cells to a lytic state of infection. Rta is required for viral replication during EBV activation and regulates EBV DNA replication and transcription. It has been shown that RTA activates a signal transduction cascade of BZLF1 transcripts to induce lytic EBV infection [58]. Together, the viral transcription factors Rta and Zta mediate the transition from latent EBV infection to lytic virus replication, and they induce expression of each other.

3.2. Epigenetic regulation of the viral genome

BZLF1 expression level is crucial in determining whether EBV is a latent or reactivated type. In regulating BZLF1 induction and suppression, epigenetic modifications play a crucial role. Even though the viral genome is heavily methylated, The EBV immediate-early protein BZLF1 converts a latent infection to a lytic infection, and this may be because EBV has evolved a mechanism that maintains a small amount of CpG methylation in the Zp region while maintaining high levels of methylation in other lytic promoters. Therefore, a small amount of CpG methylation in the Zp region allows Zp to readily activate the transcription of BZLF1 [59,60].

Besides, Jenkins et al. showed that changes in histone acetylation of the BZLF1 gene promoter appear to be a vital part of the EBV reactivation mechanism [61]. Similarly, Chang et al. demonstrated that acetylation of histones in the Rp region activates the transcription of

BRLF1. The activation is essential for the development of EBV lysis. Histone H3K9 acetylation (H3K9ac), histone H4K8 acetylation (H4K8ac), and histone H3 Lys27 acetylation (H3K27ac) are the local acetylation states of histones H3 and H4 around Zp and Rp, affect the formation of an open chromatin conformation [62]. BZLF1 is essential for the reactivation of EBV from latency due to its distinct properties.

3.3. Cellular signaling pathways involved in EBV reactivation

PKC, NF-κB, p38 MAPK, PI3K, and ERK signaling pathways have been implicated with EBV reactivation in recent research [63]. PKC that has been activated interacts with signaling pathways that regulate cell differentiation and survival, including c-Jun, MEK-ERK, Raf1 [64], NF-κB, STAT1, and STAT3 [65]. PKC theta (PKC), a member of the novel class of PKCs, has been shown to have a role in TPA-mediated NF-κB activation in B cells by controlling the activation of MKK4, a kinase that works in T lymphocytes upstream of JNK MAPK and p38. TPA can effectively induce the EBV lysis cycle in cells by strongly activating PKCs [66]. Matusali et al. demonstrated that inhibiting p38 MAPK prevented the EBV lytic cycle from being induced in Raji cells, suggesting an essential role of this signaling pathway in EBV reactivation [67].

Furthermore, data have demonstrated that siRNA targeting p38 MAPK blocks TPA-induced p38 phosphorylation and BZLF1 expression in EBV-positive epithelial cells [67]. According to Nanb et al., lytic induction and cell-to-cell EBV transmission were both suppressed by ERK and NF-κB pathway inhibitors. Blockade of the PI3K pathway and knockdown of RelA/p65 impaired EBV dissemination and inhibited lysis induction. These findings demonstrate that ERK, PI3K, and NF-κkB pathways are involved in the viral lytic activation of BL and epithelial cells co-cultured with EBV [68]. These signaling pathways ultimately trigger the latent-lytic switch by activating some Zp and Rp transcription factors.

3.4. In vitro lysis cycle activation

In cell model systems, a variety of biological factors cause lysis reactivation. These include DNA methyltransferase inhibitors(e.g., azacitidine), protein kinase C agonists (e.g., phorbol 12-myristate 13-acetate), anti-immunoglobulins, transforming growth factor β and HDAC inhibitors(e.g., sodium butyrate) [69–71], which induce stimulation of Zp activation, thereby allowing EBV to enter lysis.

Chemotherapeutic agents such as gemcitabine, adriamycin, cisplatin, paclitaxel and 5-FU [72,73], both gemcitabine and doxorubicin activate the transcription of the promoters of two immediate-early (IE) genes BZLF1 and BRLF1. The BRLF1 promoter's EGR-1 motif, as well as the BZLF1 promoter's CRE (ZII) and MEF-2D (ZI) binding sites, are necessary for this effect [72]. In contrast, cisplatin, 5-fluorouracil (5-FU), and paclitaxel cause EBV infection to switch from latent to lytic in tumor cells by activating the signaling pathways for protein kinase C delta, phosphatidylinositol 3′-kinase, and p38 stress mitogen-activated protein kinase [73].

Besides pharmacological agents, hypoxia and reactive oxygen species have also been shown to activate the lysis cycle. The transcription and protein expression of the BZLF1 gene are both elevated in response to hypoxia, and this effect is time-dependent [74]. It also induces a 3.5-fold activation of Zp [75]. A hypoxia response element (HRE) in the promoter of the EBV latent-lytic switch BZLF1 gene, Zp, is bound by the hypoxia-inducible factor 1 (HIF-1) in EBV-infected cells, promoting EBV from latent infection to lytic state [76–78].

By binding to the Sp1 binding element in Zp and Rp, reactive oxygen species (ROS) inducers and hydrogen peroxide trigger the lytic cycle [79]. In addition, other stressors, such as radiation-induced oxidative stress, convert latent EBV infection to a lytic form by inducing BZLF1 gene expression [80,81]. Previous studies have found that oxidative stress induces BZLF1 gene expression and contributes to the reactivation of the EBV lytic cycle [82]. According to Huang et al., Several signaling pathways are activated by oxidative stress, such as ATM, p38, and JNK, and are also responsible for the p53-dependent induction of EBV reactivation [83].

4. EBV lytic reactivation promotes tumorigenesis

The role of latent EBV infection in generating tumors has received a lot of attention in the past research [84–88]. Reactivation of the EBV has reportedly been linked to EBV-associated tumor growth in recent years. High viral load and elevated antibody to EBV lytic products serve as indicators of diagnostic [89], disease prediction, therapeutic efficacy estimation [90,91], and prevention [92] of many diseases, including Infectious mononucleosis [93,94], EBV-positive Hodgkin's lymphoma [95], extranodal natural killer/T-cell lymphoma [95], transplant lymphoproliferative disorder [96–98], and nasopharyngeal carcinoma (NPC) [99–102]. It has been shown that EBV antibody titer fluctuations occur before the onset of nasopharyngeal carcinoma [103,104]. Viral strains isolated from patients with nasopharyngeal carcinoma (NPC) [105] or gastric cancer [106] have higher levels of spontaneous lytic replication in B cells and epithelial cells compared to common strains.

Reactivation of EBV is marked by the continuous expression of lytic proteins, lysis of infected cells, and production of new infectious viruses [107]. In this section, we will describe how the EBV lytic phase promotes tumor malignancy in terms of both EBV lysis proteins and viral particles.

4.1. EBV-associated lytic proteins and their contribution to tumor progression

EBV lytic gene products, including immediate early lytic genes (BRLF1 and BZLF1), early lytic genes (BHRF1, BALF1, BALF3, BARF1, BGLF4, BGLF5, and BMRF1) and late lytic genes (BcLF1 and BLLF1), have been shown to contribute to the acquisition of cancer hallmarks [108,109]. Fig. 2.

EBV lytic reactivation contributes to genomic instability, immunosuppression, maintenance of proliferative signaling, activation of metastasis, promotion of tumor-promoting inflammation, and induction of angiogenesis. The increased production of lytic proteins and the subsequent increase in EBV-infected cells create a microenvironment that favors the development and progression of cancer.

4.1.1. Genome instability

Genomics instability (GI) is one of the major factors of oncogenic transformation [110,111]. Repeated EBV reactivation causes the development of micronuclei (a sign of genomic instability) and DNA double-strand breaks in nasopharyngeal cancer cells [112]. Several early lytic proteins contribute to the genomic instability in EBV-infected cells. In the early stages of EBV infection, the expression of ZEBRA induces oxidative stress in purified B cells and epithelial cells, which increases genomic instability [82,113–115]. The immediate-early gene BRLF1 also induces chromosome missegregation in NPC cells and genomic instability by activating Erk signaling pathway [116]. In addition, BALF3 promotes genomic copy number aberrations and tumorigenic features in NPC cells [117]. The early lytic gene BGLF4 protein kinase causes structural chromosomal abnormalities and micronucleus formation [118]. Cohesin SMC5/6 plays major roles in chromosome maintenance and DNA damage repair [119]. Late gene BNRF1 depletes SMC5/6 complexes and contributes to DNA damage [120]. Moreover, the BGLF5 nuclease (EBV DNase) induces DNA damage signaling and inhibits the transcription of DNA repair enzymes by inducing micronucleus formation and phosphorylation of H2X [118].

4.1.2. Avoiding immune destruction

Lysis antigens may promote immune evasion and immune regulation by inducing inflammation-associated cytokine expression, inhibiting immune cell function, and downregulating antigen presentation by MHCs. The transcription factor Zta contributes to the secretion of the

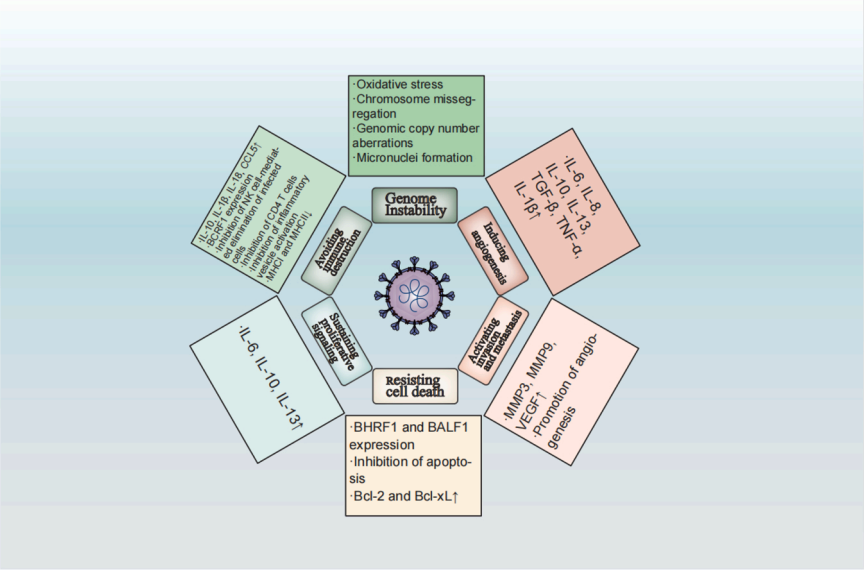

Fig. 2. The role of EBV lytic activation in malignant tumor progression.

immunosuppressive cytokine interleukin-10 (IL-10) [121]. BRLF1 inhibits inflammatory vesicle activation and host antiviral response. Moreover, when BRLF1 is inhibited, viral infection can induce activation and killing of NK cells and T cells through upregulation of IL-18 and IL-1β [122]. Viral interleukin-10 (vIL-10) is a homolog of IL-10 and is encoded by the early lytic gene BCRF1 [123]. It interferes with CD4 + T cell activity, inhibits NK cell-mediated killing of infected B cells, and regulates cytokine responses[124].

Mitochondria serve as critical nodes in the innate immune response against viruses. BHRF1 can reduce interferon induction and prevent innate immune activation by causing mitochondrial fission [125,126]. EBV-transformed lymphoblastoid cell lines (EBV-LCLs) produce higher levels of CCL5 and IL-10 when activated [127]. These cytokines may inhibit the immune regulation of cytotoxic lymphocytes and recruit immunosuppressive myeloid cells [128]. Studies have shown that CCL5 attracts monocytes to the Hodgkin lymphoma microenvironment and that their immunosuppressive activity promotes tumor growth in xenograft models [129]. Reactivation of EBV resulted in increased programmed cell death-ligand 1 (PD-L1) expression, which is critical for tumor immune escape and host T cell exhaustion [130].

BGLF5 inhibits the synthesis of HLA class I and class II molecules. It reduces antigen-presenting complexes on the cell surface of EBV lytic cycles, inhibiting T cell recognition and elimination of EBV-producing cells [131]. BILF1 enhances the degradation of major histocompatibility complex class I (MHC-I) antigens through lysosomes [132].

BZLF2, which encodes viral glycoprotein 42 (gp42), suppresses antigen presentation mediated by MHC II [133]. BDLF3, which encodes glycoprotein 150 (gp150), ubiquitinates and represses the expression of MHCI and MHCII [134]. BNLF2a encodes an inhibitor of a transport protein associated with antigen processing that reduces antigen presentation and inhibits the recognition function of CD8+ T cells [124].

4.1.3. Resisting cell death

BALF1 and BHRF1 are two EBV early lytic genes. They are highly expressed in DLBCL and encode viral Bcl-2 homologs that immortalize B cells [135–137]. By suppressing the pro-apoptotic cellular proteins PUMA, BIM, BID, and BAK112, BHRF1 exerts anti-apoptotic actions [138]. Induction of BHRF1 expression shields BL cells from apoptosis and enhances EBV-associated lymphoma development in vivo [139]. BALF1 has been shown to play an important role in EBV-associated tumorigenesis by increasing cell survival through inhibition of serum starvation-induced apoptosis and upregulation of expression of Bcl-xL and Bcl-2 [140].

Zta has been reported to downregulate TNF receptor 1 (TNF-R1) to inhibit tumor necrosis factor α (TNFα)-induced apoptosis [141]. BMRF1 is essential for the lysis replication of the EBV genome [142]. Inhibition of the expression of the early gene BMRF1 and the immediate early gene Zta using arsenic trioxide led to the death of EBV-positive lymphocytes [143].

4.1.4. Sustaining proliferative signaling and enabling replicative immortality

EBV Lytic infection promotes lymphoproliferative diseases through enhanced expression of paracrine B-cell growth factors IL-6, IL-10 [144], and IL-13 [145,146], in which two EBV IE proteins (BRLF1 and BZLF1) play an important role. IL-6 has a crucial pathogenic function in EBV-associated B-lymphoproliferative disorder(BLPD). A clinical study confirmed that anti-IL-6 antibody treatment relieves symptoms associated with BLPD [147]. BHRF1 expression contributed to the survival of tumor cells and accelerated the development of lymphomas [138].

4.1.5. Activating metastasis and angiogenesis

Endogenous BZLF1 promotes migration and invasion of EBV-infected cells by inducing MMP3 expression [148]. Hong et al. reported that EBV lysis of infected cells induced expression of BZLF1 might promote angiogenesis and thus malignant tumor progression [149]. BRLF1 upregulates MMP9 [150] and induces IL-6 [151] expression to promote the migration of nasopharyngeal carcinoma cells. BALF1 transfectants exhibit significantly increased tumor metastasis [152]. In a constitutively active manner, BILF1 can transform cells and promote VEGF secretion [153].

4.1.6. Tumor-promoting inflammation

Inflammation can promote the development of cancer and tumorigenesis at all stages [154]. As previously mentioned, EBV lytic infection fosters the expression of IL-6, IL-10 [144] and IL-13 [145,146]. The immediate early lytic protein Zta induces IL-8 expression in NPC cells and increases IL-8 secretion [155]. Zta also increases the level of TGF-β mRNA, and the amount of active TGF-β secreted into the culture medium [156]. The EBV-encoded dUTPase (BLLF3) promotes the expression of several different pro-inflammatory cytokines, including TNF-a, IL-1β, IL-6, IL-8, and IL-10, thereby inducing immune dysregulation [157].

The complete lytic phase of EBV and tumor progression seem to be inconsistent. Once the lytic phase is complete, the cells will perish and

stop contributing to tumor hallmarks such as genomic instability, avoiding immune destruction, maintaining proliferative signals, and resisting cell death. In this regard, cells that experience an incomplete (abortive) lytic phase play a crucial role, as cells in this phase express early lytic genes but do not produce new infectious particles. It has been reported that in SCID mice, effective tumor formation does not require the release of infectious viral particles. Even if EBV replication is inhibited, early lytic viral gene expression can promote tumor progression [144].

On the other hand, lysis of cells infected with EBV can promote the formation of a tumorigenic microenvironment by inducing the cell signaling molecules, expression of growth factors, and pro-inflammatory cytokines that promote genomic instability, angiogenesis, and cell proliferation. Additionally, by increasing the number of latently infected cells, cells that complete the lytic phase may impact surrounding cells and contribute to the development of tumors.

4.2. Virus replication and virus particle release

EBV lysis infection increases the total number of latently infected cells by enhancing the spread of the virus between cells, increasing the probability of cellular carcinogenesis [158]. Radiotherapy is a routine treatment for nasopharyngeal carcinoma. Ten to thirty percent of patients with nasopharyngeal cancer have persistent plasma EBV DNA after radiation or radiotherapy. These individuals have a higher chance of treatment failure [159]. There is also a substantial correlation between plasma EBV DNA clearance after radiation and the absence of clinical progression [160]. This suggests plasma EBV DNA after radiotherapy may be associated with poor patient prognosis. Patients with EBV-associated gastric cancer have been reported to have significantly higher IgG and IgA antibody titers against EBV capsid antigens more than five years before diagnosis [161], suggesting that EBV reactivation produces lytic viral proteins occurs prior to the development of EBV-associated gastric cancer. EBV particles can induce chromosomal instability. Furthermore, genetic and transcriptomic analyses support the shift to the lytic phase in Epstein Barr virus infection as an essential driver in the development of SLE [162].

5. Treatment options related to EBV lysis

Given the role of EBV lytic activation plays in tumor progression, inhibition of EBV lytic replication in the setting of EBV-associated malignancies might improve treatment outcomes. The primary effect of inhibiting the lytic replication of EBV is to reduce the viral load of EBV and reduce the risk of lymphoma due to chromosomal translocations [163].

5.1. Antiviral drugs

Several antiviral drugs and compounds have been to block virus transmission by inhibiting EBV reactivation. Some of them may be effective in controlling EBV tumors in combination with lysis-inducing strategies.

5.1.1. Nucleoside analogues

Studies have shown that nucleotide analogs can inhibit EBV lytic replication. Several drugs are currently under investigation for EBV infection treatment, including acyclovir, ganciclovir, omaciclovir, and Maribavir [3]. After EBV enters the lytic phase, two kinases, EBV thymidine kinase and the BGLF4 gene product, are produced [164]. These two proteins convert antiviral nucleotide analog prodrugs, such as ganciclovir (GCV), into active forms converted to nucleotides and integrated into viral DNA to kill EBV host cells [165–167]. By interfering with host DNA polymerases, phosphorylated GCV causes early cessation of DNA replication and tumor cell death, exposing EBV to host immune surveillance [168]. Additionally, the active medication might be spread to neighboring cells and kill these cells by the "bystander effect" [169]. A study demonstrated that 15 EBV-related malignant lymphoma patients was treated by arginine butyrate in combination with ganciclovir, as a result two thirds of them showed significant antitumor responses. Given this, lysis induction therapy is a new treatment strategy now under development and uses nucleoside analogs in conjunction with EBV lysis inducers [170].

5.1.2. Valproic acid (VPA)

VPA is a short-chain fatty acid HDAC inhibitor. Sodium butyrate (NaB) is an endogenous HDAC inhibitor that promotes the activation of EBV lysis. However, unlike sodium butyrate, VPA and its amide derivative Valpromide (VPM) can cause hyperacetylation of histone H3 and inhibit the induction of the early EBV lysis proteins ZEBRA and EA-D in response to epigenetic modifiers such as NaB. Additionally, it reduced EBV's reaction to anti-IgG in Akata cells and tetradecanoyl phorbol acetate (TPA) in Raji cells. In addition, VPA stimulates the expression of numerous cellular genes, including MEF2D, YY1, and ZEB, which suppress the EBV lytic cycle [71,171]. However, the mechanism by which VPA and VPM act as an inhibitor of EBV reactivation is still under investigation. Since they can target the activation of latency and viral late protein expression, studies have demonstrated their potential for treating diseases associated with lytic replication [172]. Maarten A. Wildeman et al. [173] developed a new therapy called cytolytic virus activation (CLVA) therapy which comprising gemcitabine (GCb), VPA, and GCV, and also, Sharon D. Stoker et al. [174] used a combination of gemcitabine (GCb) and valproic acid (VPA) to treat patients with undifferentiated nasopharyngeal carcinoma (NPC). The result is that the condition of most patients has significantly improved after about 10 months of treatment.

5.1.3. Rapamycin

Rapamycin interacts with FKBP-12 and is a selective inhibitor of the mTOR kinase of mTORC1. The application of rapamycin modifies the transcript levels of the immediate early proteins Z and R [175]. In epithelial cells and the opposite effect of rapamycin in B cells, the former promotes EBV lytic replication and inhibits lytic replication [176].

5.1.4. Mitochondrial protein

Zhang's team [177] discovered a mitochondrial protein, TBRG4, that affects the lytic activation of EBV virus. They caused a reduction of ROS in the cells by knocking down the TBRG4 gene of cells, which targeted LMP1 mediated reduction of oxidative stress and thus increased EBV lytic reactivation. It is worth investigating whether this protein, in combination with the drugs mentioned above, kills the virus in the lytic phase, becoming a new therapeutic modality.

5.1.5. Natural compounds

Many natural compounds have also been reported to inhibit the lytic replication of viruses. Polyphenol(-)-epigallocatechin-3-gallate (EGCG) is a polyphenolic compound extracted from green tea. EGCG can inhibit LMP1 and its downstream signaling molecules to decreases the phosphorylation or activation of extracellular signal regulated kinase 1 / 2 (ERK1 / 2) and serine / threonine protein kinase (Akt). It also leads to abnormal expression of many transcription factors, including nuclear factor-κb and activator protein-1(AP-1), resulting in the aberrant expression of multiple transcription factors making the ZII element in the BZLF1 gene promoter abnormal [176]. Curcumin interferes with BZLF1 gene transcription [178]. The mechanism of action and effect of resveratrol is similar to EGCG, inhibiting NF-κB and AP-1 activation and inhibiting EBV lysis replication, reducing viral load, and reducing malignancy [179]. In general, In general, flavonoids suppress viral replication by targeting on viral or host cell components [180]. Yu Chi Tsai isolated two flavonoids from crustaceans that can affect RTA expression and thereby inhibit lytic replication [180]. In the experiment, protocerebrosidone and its analog protocerebrosidone 1′-O-isopropyl ether

inhibited Rta protein expression and lysis replication [181]. Lignans reduce EBV lytic replication by inhibiting the promoter activity of the BZLF1 and BRLF1 genes [182].

5.2. Newly discovered targets

In addition to the recognized chemicals or medications that inhibit EBV lytic replication, several recent studies have found additional targets and pathways.

5.2.1. EBV-specific cytotoxic T lymphocyte (CTL) therapy

CTL therapy is a successful treatment for people with recurrent nasopharyngeal cancer. CTL can travel actively through the microvascular wall, self-expand upon encountering tumor cell target antigens and destroy tumors via a cascade of cytotoxic effectors [183]. Lysis-specific-antigenic CD8+ CTL responses can be detected in α and β subfamilies of herpesviruses [183], CTL of viruses such as HSV and CMV, but do not target antigens of the lytic cycle, but instead produce proteins that impede the route of antigen presentation to CD8 + cells [184,185]. Steven et al., through clonal analysis, found that EBV infection induces a $CD8^+$ CTL response to the immediate and early proteins, suggesting that EBV lytic replication is under direct CTL control [186]. All this evidence demonstrates that EBV lytic replication-phase proteins can be new targets for CTL therapy [187].

5.2.2. Vaccines

Therapeutic vaccines to treat EBV-associated malignancies may also be an effective treatment. The research on the EBV vaccine mainly focuses on the virus glycoprotein (gp350), the most in-depth one [188–190]. Similarly, latency and lytic proteins also serve as candidates for the EBV vaccine. Longnecker et al. demonstrated that EBV immediate early proteins ZTA and RTA had been expressed before the expression of most immune escape genes that inhibit T cell response. They were the earliest expressed genes in the process of infection [191]. Human viral infection produces BMLF1 and BMRF1 in the short term. CD4 + and CD8 + cells can target these proteins before viral structures are incompletely formed. CD4 + T cells can detect these proteins early after the viral invasion of humans[192]. Hartlage and colleagues found that when mice were given dendritic cells that expressed the Zta protein, the mice produced a T-cell response specific to Zta and experienced a delay in the onset of EBV lymphoproliferative disease [193,194].

5.2.3. Regulation of host genes

Recent studies identify both MYC or a reduction in factors that promote MYC generation may reactivate the lytic cycle. MYC overexpression at the level of BZLF1 inhibits lytic replication [195]. Maintaining stable expression of the MYC gene may inhibit the process of EBV lytic replication. STAT3, a transcription factor that is hyperactive in many cancers [196]. It can regulate sensitivity to the lytic cycle; activation signals by regulating PCBP2, a protein important in RNA biogenesis, and suppression of PCBP2 levels is sufficient to increase the number of EBV lysed cells [197].

5.2.4. N^6 methyladenosine (m^6A) modification

N6 methyladenosine (m^6A) modification is the most prevalent protein-coding RNA modification [198]. Inhibition of m6A methylation reduces viral lytic protein expression, inhibiting progeny virion formation [199–201]. According to the mechanism reported by Dipayan Bose et al. [202], furthermore, the inhibition can increased production of IFN. Increased IFN expression can enhance the host's antiviral response. The METTL3 gene and protein or compounds that inhibit m6A modification can all be potential targets for new anticancer drugs in combination with lysis inducers[203].

5.2.5. Gut microbiota

Interestingly, an article mentioned that gut microbiota affects the fermentation of undigested starch and non-starch polysaccharides in the intestine, affecting the formation of short chain fatty acids in the intestine [66]. A study had reported that short chain fatty acids have a promoting effect on the cleavage cycle of EBV [204]. Further research on gut microbiota may promote the development of new treatments for EBV related- tumors.

6. Conclusion

More than 95 % of healthy persons have asymptomatic EBV infection, but only a small percentage develop malignant tumors [52]. These observations motivated us to investigate if EBV reactivation played a significant role in EBV-associated carcinogenesis. This review covers information about the EBV life cycle and reactivation with tumors and current therapies for EBV-associated tumors. In the host cell, EBV has developed a complicated life cycle that increases its chances of survival. Epigenetic regulation, signal transduction, and several in vivo and in vitro stimuli promote EBV lysis. During EBV reactivation, the production of its lysis proteins fosters the development of many EBV-associated tumors. Consequently, drugs such as VPA and nucleotide analogs are used to block lysis activation and replication to provide alternative strategies against EBV-positive cancers. However, the current application of oncolytic therapy [205] is now used to cause lysis of tumor cells by inducing viral lysis and stimulating the body to produce a specific tumor immune response [206]. Although this lysis-inducing therapy appears promising, it can have significant side effects when lysis-inducing agents or antiviral drugs do not work effectively enough [207,208]. A better understanding of the mechanisms driving EBV reactivation and the pathogenic role of EBV lysis in carcinogenesis could contribute to development of innovative therapeutics for EBV-associated malignancies.

CRediT authorship contribution statement

Dr. Xiaoming Lyu for providing guidance and support throughout the project. Haiqi Tan, Yibing Gong, Yi Liu, Jingyi Long mainly wrote this manuscript. Yi Liu drew the schema diagram. Qingshuang Luo, Oluwasijibomi Damola Faleti and Xiaoming Lyu read and made revisions to the manuscript. All authors of this paper have read and approved the final version submitted.

Declaration of Competing Interest

All authors of this paper have read and approved the final version submitted And the authors declare no conflict of interest The funding organization(s) played no role in the study design; in the collection, analysis, and interpretation of data; in the writing of the report; or in the decision to submit the report for publication.

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