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Review

Epstein-Barr virus: Biology and clinical disease

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SUMMARY

Epstein-Barr virus (EBV) is a ubiquitous, oncogenic virus that is associated with a number of different human malignancies as well as autoimmune disorders. The expression of EBV viral proteins and non-coding RNAs contribute to EBV-mediated disease pathologies. The virus establishes life-long latency in the human host and is adept at evading host innate and adaptive immune responses. In this review, we discuss the life cycle of EBV, the various functions of EBV-encoded proteins and RNAs, the ability of the virus to activate and evade immune responses, as well as the neoplastic and autoimmune diseases that are associated with EBV infection in the human population.

INTRODUCTION

Epstein-Barr virus (EBV), also known as human herpesvirus 4 (HHV-4), is a member of the gammaherpesvirus family. EBV belongs to the gamma 1 or lymphocryptovirus genus and was identified as the first human tumor virus. EBV was first discovered in 1964 in Burkitt lymphoma (BL) and was later found to also be associated with other types of lymphoma including Hodgkin lymphoma (HL), non-HL in post-transplant patients and HIV-infected individuals, T cell lymphoma, and natural killer (NK)/T cell lymphoma (Gewurz et al., 2021) (Table 1). EBV is also associated with epithelial cancers including nasopharyngeal carcinoma (NPC) and a subset of gastric cancers (Table 1). In addition to its association with different forms of human cancer, EBV is also linked with non-malignant disease including infectious mononucleosis (IM), oral hairy leukoplakia, systemic lupus erythematosus (SLE), and multiple sclerosis (MS).

EBV infects over 95% of the world's population and is a highly successful pathogen. Primary infection is often asymptomatic and occurs at a young age in developing countries and at a later age in more industrialized countries (Gewurz et al., 2021). EBV is intermittently shed in saliva in healthy individuals. In the USA, the seroprevalence of EBV antibody ranges from 50% in children to 89% in teenagers (Lunn et al., 2017). When primary infection occurs after childhood, it can result in IM (Vedham et al., 2015). EBV transmission primarily occurs through saliva. However, breast milk, bodily fluids, and transplantation of EBV-positive organs can also spread the virus from one host to another. There are two types of EBV isolates—type 1 and type 2, which have sequence polymorphisms in the EBV nuclear antigen 2 (EBNA2) and EBNA3 genes. Type 2 EBV has decreased lymphocyte transformation capacity (Tzellos et al., 2014). Coinfections with both type 1 and type 2 isolates can occur.

EBV establishes life-long persistence in the human host by infecting B cells and residing in memory B cells in healthy people where it is asymptomatic and does not cause disease. However, both intrinsic factors (e.g., genetic mutations and deficiencies) and extrinsic factors (e.g., immunosuppression, HIV infection, salted or preserved fish diet) can result in the development of EBV-associated cancers.

Similar to other herpesviruses, EBV has two distinct phases of its life cycle—latency and lytic replication. During the latent phase, the virus is present in the nucleus as a circular episome tethered to the host genomic chromatin utilizing a viral protein named EBNA1. Under latent conditions, the virus expresses a small fraction of viral genes and non-coding RNAs and, depending on the cell type infected, distinct latent gene expression programs have been observed. During latency, the virus is dependent on normal cellular division processes, including the host DNA replication machinery, to passively replicate its viral genome and be transmitted to daughter cells.

Latency is a hallmark of EBV, and the virus establishes life-long latency in humans with only sporadic episodes of reactivation and lytic replication. Under certain conditions, the virus is able to reactivate and enter the lytic cycle where all viral genes are expressed, and the virus can replicate its viral genome and produce infectious progeny viruses. Lytic replication typically results in cell death and release of infectious virus that can infect naive cells in the same host or be transmitted to new hosts. However, abortive lytic expression can also occur where the virus expresses a subset of lytic genes but does not enter full blown lytic replication (Gewurz et al., 2021).

Viral entry

Saliva is the primary route of EBV transmission. EBV infects epithelial cells in the oropharynx where it can replicate and

Table 1. EBV-associated cancers, latency type, and viral gene expression

EBV-associated disease	Latency type	EBV viral gene expression
Healthy individuals (resting EBV-infected B cells)	0	EBERs, BARTs
Burkitt lymphoma (BL)	I	EBERs, BARTs, EBNA1
Gastric carcinoma	I or II	EBERs, BARTs, EBNA1
Hodgkin lymphoma (HL)	II	EBERs, BARTs, EBNA1, LMP1, LMP2
NK/T cell lymphoma (NKTL)	II	EBERs, BARTs, EBNA1, LMP1, LMP2
Nasopharyngeal carcinoma (NPC)	II	EBERs, BARTs, EBNA1, LMP1, LMP2
Diffused large B cell lymphoma (DLBCL)	II or III	EBERs, BARTs, EBNA1, EBNA2, EBNA3A,B,C, EBNA-LP, BHRF1 miRNAs
HIV-associated lymphomas	III	EBERs, BARTs, EBNA1, LMP1, LMP2, EBNA2, EBNA3A,B,C, EBNA-LP, BHRF1 miRNAs
Post-transplant lymphoproliferative disease (PTLD)	III	EBERs, BARTs, EBNA1, LMP1, LMP2, EBNA2, EBNA3A,B,C, EBNA-LP, BHRF1 miRNAs

subsequently infect B cells that traffic to the oral cavity (Figure 1). Alternatively, the virus in saliva may also directly infect B cells in the oral cavity after epithelial transcytosis.

Depending on the cell type, different EBV glycoproteins participate in epithelial versus B cell infection. During B cell infection, EBV gp350/220 binds the complement receptor CD21 present on B cells, or it can also utilize another complement receptor, CD35 (Fingeroth et al., 1984; Ogembo et al., 2013). CD21 is also expressed on T cells and may be utilized to infect T cells as well (Smith et al., 2020). Although EBV infection of B cells involves gp350/220 attachment to CD21, epithelial cells lack CD21, and hence, gH is used for attachment. Following attachment, three EBV glycoproteins, gH, gL, and gp42, participate in viral entry. In B cells, entry involves the binding of gp42 to HLA class II molecules, which functions as a co-receptor, whereas in epithelial cells lacking HLA class II, entry does not require gp42 and is instead mediated only by the gH-gL complex (Borza and Hutt-Fletcher, 2002). During EBV replication in epithelial cells, gp42 binds to the gH-gL complex. However, when the virus replicates in B cells, gp42 is instead sequestered with HLA class II protein, and hence, the virus emanating from B cells lacks gp42 in the gH-gL complex, which makes this virus more efficacious in infecting epithelial cells rather than fellow B cells. In summary, virus that arises from replication in epithelial cells can efficiently infect B lymphocytes, whereas virus that originates from replication in B cells has a superior capacity to infect epithelial cells (Borza and Hutt-Fletcher, 2002). Thus, the virus appears to switch effortlessly between infection of these two different cell types.

Following entry, EBV virions are endocytosed into B cells (Tanner et al., 1987) and the membrane of the virus fuses with the endosomal membrane (Chesnokova et al., 2014). This event is mediated by EBV gH/gL and gB (Chesnokova et al., 2014). On the other hand, EBV was first thought to enter epithelial cells through direct fusion of the viral membrane with the cell membrane (Miller and Hutt-Fletcher, 1992). More recently, however, it was reported that EBV can also enter epithelial cells via lipid raft-dependent endocytosis and micropinocytosis mediated by neuropilin 1 (NRP1), which interacts with EBV gB (Wang et al., 2015). EBV gp350 or BMRF2 can mediate attachment to the epithelial cell while gB and gH/gL appear to be involved in epithelial entry and fusion (Chen and Longnecker, 2019). Host proteins involved in epithelial cell infection include integrins, NRP1, and ephrin receptor A2 (EphA2) (Chen and Longnecker, 2019). In fact, EphA2 is thought to play a critical role in epithelial cell infection (Chen et al., 2018; Zhang et al., 2018)

EBV LATENCY

Early events after infection

As described above, EBV efficiently infects B lymphocytes and establishes latency where several viral proteins are expressed through a carefully regulated and complex mechanism (Gewurz et al., 2021). The viral genome is separate from host DNA and is retained as an extrachromosomal episome wrapped in nucleosomes, a characteristic of herpesvirus latency (Gewurz et al., 2021). BNRF1, an EBV tegument protein, promotes establishment of latency through inhibition of the ATRX/DAXX complex that would otherwise deposit repressive histone complexes on the incoming EBV genome (Tsai et al., 2011).

Following infection of B lymphocytes, the EBV genome circularizes through the terminal repeats (TRs). The TR number can be used to distinguish individual cellular infections and used as a surrogate marker for cell clonality (Raab-Traub and Flynn, 1986). During cell division, the viral genome is subsequently replicated by the host DNA polymerase with replication initiated at the origin of plasmid replication (OriP) and partitioned to the daughter cells (Gewurz et al., 2021). During latency and transformation, the virus does not undergo lytic replication to produce progeny virions. The relative abundance of cellular transcription factors dictates in part the activity of viral promoters. In B lymphocytes, specific factors, including YY1 and Pax5, activate the first viral promoter, Wp, to initiate a complexly spliced mRNA transcribed through the W repeat sequence, IR1 (Gewurz et al., 2021). Through interaction

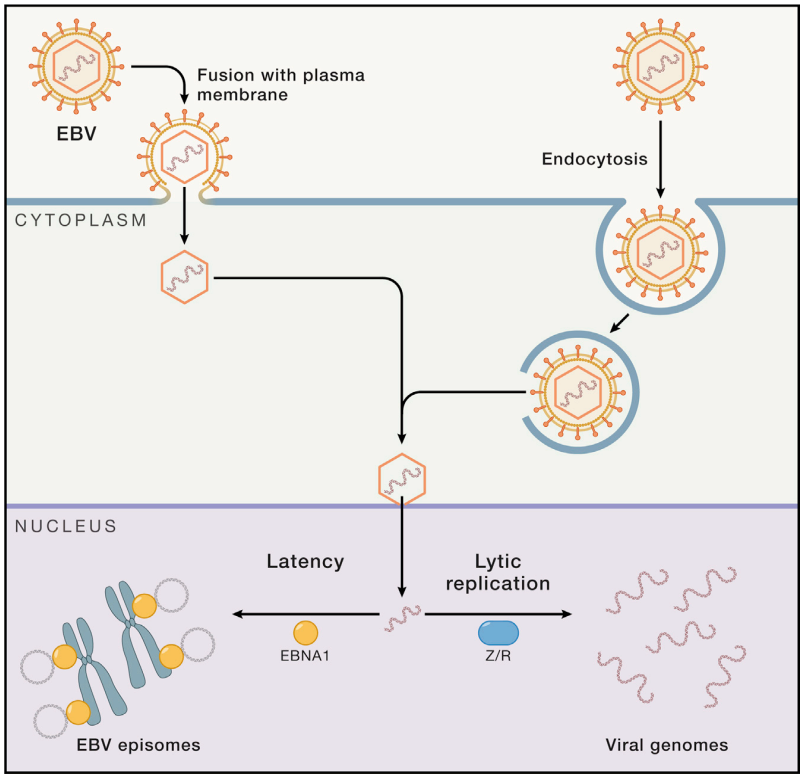

Figure 1. EBV viral entry
Virion binding, attachment, and entry into the host cell is depicted. EBV can enter either through endocytosis or fusion with the plasma membrane. After the viral genome is injected into the nucleus, the virus can either enter latency or lytic replication depending on the cell type and environmental cues.

with a host cell DNA binding protein, RBP-Jk, EBNA2 then activates the EBV C promoter (Cp). Transcription at Cp produces an approximately 125 kilobase EBV transcript, which expresses six EBNAs through alternatively splicing.

There are several types of EBV latency. Latency 0 displays expression of EBV-encoded RNAs (EBERs) and BamHI A-encoded transcripts (BARTs) and generally occurs in quiescent memory B cells. Latency I is the next most restricted pattern with expression of EBNA1, EBERs, and BARTs. Latency II displays expression of EBNA1, latent membrane protein 1 (LMP1), LMP2, the EBERs, and high levels of BART expression. The most complex and best characterized is termed latency III. Latency III displays expression of three integral latent membrane proteins (LMP1, 2A, 2B), six nuclear antigens (EBNA1, 2, 3A, 3B, 3C, and EBNA-LP), and multiple non-coding RNAs, the EBERs, BHRF1 microRNAs (miRNAs), and BARTs. It is important to note that there are also multiple subtypes with variations of a latency pattern expression where type I may sometimes include expression of LMP1 or BHRF1 and type II in some NPC may lack LMP1 expression. There are also variations in EBNA2 or 3 expression (Table 1).

VIRAL GENE PRODUCTS EXPRESSED DURING LATENCY

EBNAs

EBNA1

EBNA1 is needed for viral genome maintenance during latency. EBNA1 directly binds to OriP to enable replication of the EBV genome by the host machinery in S phase. The newly replicated viral genomes are tethered to the host genome and partitioned to daughter cells. OriP contains a family of repeats (FR), a dyad symmetry (DS) element, and two *cis*–acting elements that are critical for the retention of EBV episomes. FR contains multiple 18 bp copies of an EBNA1 recognition sequence and functions as an enhancer (with EBNA1) that is important for activation of Cp and expression of all of the EBNAs (Gewurz et al., 2021). EBNA1 also binds to and regulates certain cellular genes and links the EBNA1/FR-bound episomes to condensed mitotic chromosomes (Gewurz et al., 2021). The actual origin of DNA synthesis resides within the DS element. DS contains four EBNA1 recognition sites and a 65 bp region of DS and is essential for EBNA1 dependent plasmid replication. Recently, EBNA1 inhibitors have been shown to prevent EBV latency and tumor proliferation (Messick et al., 2019) in pre-clinical models.

EBNA2

EBNA2 was the first viral protein shown to be essential for B-lymphocyte growth transformation. EBNA2 is the major viral regulator of latent viral promoters and utilizes the DNA binding protein RBP-Jk to activate transcription. Binding of EBNA2 changes the activity of RBP-Jk from a repressor to an activator, suggesting that EBNA2 mimics Notch-like signaling. Expression profiling has identified many genes that are regulated by EBNA2, and ChIP-seq has determined that thousands of sites are occupied by EBNA2 and RBP-Jk. Intriguingly, EBNA2 has been shown to bind to hundreds of super-enhancer sites which then loop between distal sites and regulate concomitant expression of multiple cellular genes (Gewurz et al., 2021).

EBNA-LP

EBV nuclear antigen leader protein (EBNA-LP) is produced by an RNA that contains differing numbers of copies of the W repeat open reading frames (ORFs) and two exons from the BamHI Y fragment. LP is produced with EBNA2, to which it binds and functions as a coactivator (Gewurz et al., 2021). LP localizes with promyelocytic leukemia (PML) nuclear bodies and is thought to modulate chromatin structure through effects on histone acetylation (Ling et al., 2005). Recent analyses suggest that EBNA2 may loop super-enhancers to promoters bound by LP.

Interestingly, LP is required for efficient transformation of B cells (Mannick et al., 1991).

EBNA3 A, B, and C

The EBNA3 proteins are produced by alternate splicing of the long Cp-initiated mRNA. Importantly, it was determined that they each bind RBP-Jk (Robertson et al., 1996). The proteins share several domains and each EBNA3 possesses the ability to repress transcription. Like most of the EBV latency proteins, EBNA3A, 3B, and 3C do not have homology to host proteins. EBNA3s compete with EBNA2 for binding to RBP-Jk and can repress EBNA2 transactivation. They also can repress transcription through association with and assembly of host repressor complexes. EBNA3A also inhibits apoptosis through effects on expression of MCL-1 and BFL-1 (Price et al., 2017). EBNA3A and 3C promote proliferation and inhibit senescence by blocking expression of p16 and p14 (ARF), and EBNA3C is required for transformation of B lymphocytes unless the p16 gene is deleted (Styles et al., 2017). EBNA3A and 3C also inhibit plasma cell differentiation by decreasing PRDM1 expression (Pei et al., 2017)

LATENT MEMBRANE PROTEINS

LMP1

LMP1 is required for *in vitro* B cell transformation and is the first viral protein that transformed cultured cells. LMP1 gene expression has been detected in many EBV associated cancers including post-transplant lymphoproliferative disease (PTLD), HL, and NPC. LMP1 is enriched in lipid rafts in the plasma membrane of lymphocytes and within endosomes. Characterization of proteins that bind to LMP1 identified molecules subsequently shown to interact with tumor necrosis factor receptors (TRAFs) and suggested that aggregation from its multiple membrane spanning domains allows LMP1 to function as a constitutively active member of the tumor necrosis factor receptor (TNFR) family (Miller et al., 1998) (Figure 2A). The TRAFs bind to two regions within the long C-terminal domain of LMP1, C-terminal activating region 1 (CTAR1) and CTAR2. These domains bind distinct TRAFs and have unique properties. The two domains and the specific TRAFs suggest that LMP1 most closely mimics CD40 (Hatzivassiliou et al., 1998). CTAR2 activates the canonical NF-κB pathway and formation of p50/p65 complexes and activation of c-Jun N-terminal kinase (JNK) through interactions with adapter proteins and TRAF6. CTAR1 activates canonical and noncanonical NF-κB pathways resulting in distinct NF-κB dimers (e.g., p50/50, p52/p65, and p52/p50) (Gewurz et al., 2012; Luftig et al., 2003). CTAR1 also activates PI3K and upregulates epidermal growth factor receptor (EGFR) expression (Mainou et al., 2007). Induced p50-Bcl-3 complexes can bind to NF-κB consensus motifs on the EGFR promoter (Edwards et al., 2015). A third domain that contains the TRAF motif (CTAR3) interacts with the small ubiquitin-like modifier (SUMO)-conjugating enzyme, UBC9 (Bentz et al., 2011).

Exosomes are small vesicles containing proteins and RNA that are released from cells (Raab-Traub and Dittmer, 2017). EBV-infected cells secrete LMP1-containing exosomes that inhibit peripheral blood mononuclear cell proliferation. NPC cells secrete exosomes that contain LMP1 and galectin 9, a protein that induces T cell death (Klibi et al., 2009). LMP1 upregulates secretion of exosomes containing fibroblast growth factor and EGFR. The purified exosomes containing LMP1 and EGFR are taken up by epithelial, fibroblast, and endothelial cells leading to the activation of PI3K/Akt and ERK pathways (Meckes et al., 2010). Thus, exosomes secreted from EBV-infected cells can alter proliferation of neighboring and distant cells (Raab-Traub and Dittmer, 2017).

LMP2A

LMP2A is also an important signal transducer in EBV-infected cells that oligomerizes in lipid rafts and in B cells can mimic a constitutively activated B cell (ABC) receptor (BCR) and also transduce downstream signaling including the NF-κB pathway (Longnecker and Miller, 1996). It contains several SH2 domains that can bind Src family kinases such as Lyn in B cells, an immunoreceptor tyrosine-based activation motif (ITAM) that interacts with Syk kinase, and PY motifs that interact with the Nedd4 family of ubiquitin ligases (Figure 2B). ITAM activation results in the phosphorylation and activation of Akt, inhibition of GSK3b and subsequent activation of β-catenin signaling. This prevents differentiation of epithelial cells. LMP2A can also transform epithelial cells, inhibit anoikis, and promote migration and anchorage independence through the function of its ITAM and the PY domains (Fotheringham and Raab-Traub, 2015). LMP2A expression in B cells in transgenic mice allows survival of B cells in the absence of a functional BCR and affects Btk, Erk, and Notch signaling (Anderson and Longnecker, 2009). *In vivo*, its consistent expression at high levels in Reed-Sternberg cells in HL- and EBV-related carcinomas confirms its important role in latency and pathogenesis.

VIRAL NON-CODING RNAs

EBERs

The small nuclear EBER RNAs, EBER1 and EBER2, are the most abundant RNAs in EBV-infected cells (Gewurz et al., 2021), with approximately 10^5 copies per cell. The EBERs are expressed during all the different latency states and are used as a marker for latently infected cells. They are transcribed by RNA polymerase III, and also tightly bind the La protein, suggesting that they may affect pol III transcripts. They are primarily nuclear although interactions with important cytosolic proteins have been described. Although not essential for B cell transformation, the EBERs likely contribute to maintenance of latency and transformation (Swaminathan et al., 1991). EBER2 has been shown to increase expression of the UCHL1 deubiquitinase, which likely aids transformation (Bentz et al., 2014; Li et al., 2021).

BARTs

EBV expression in NPC includes high-level transcription of a family of rightward transcripts from the *Bam* HIA region that are expressed at lower levels in lymphoid cell lines (Gilligan et al., 1991). The *Bam* HIA transcripts (also called BARTs or CSTs) are differentially spliced and generate RNAs that are 3′ co-terminal. The C15 NPC tumor transcripts display alternate splicing of at least seven exons that form several potential ORFs; however, none of these proteins have been confirmed.

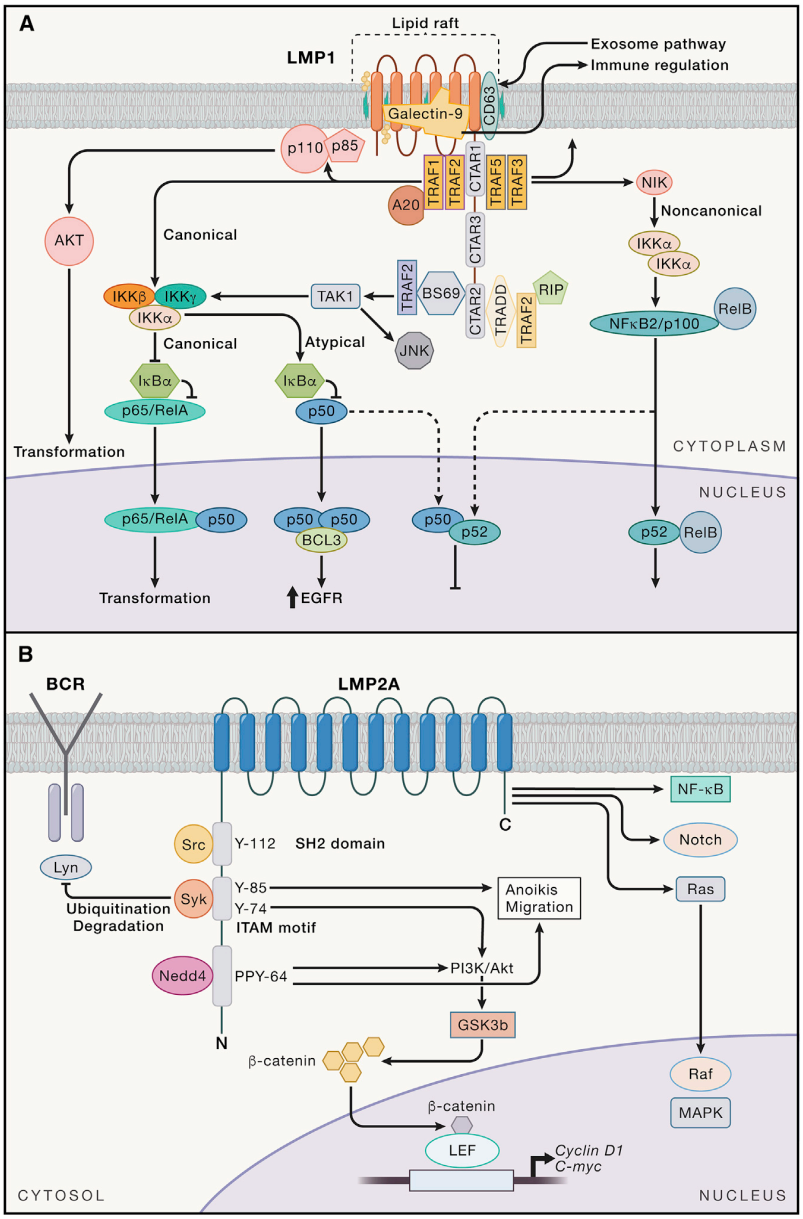

Figure 2. Molecular interactions and activation of cell signaling pathways by LMP1 and LMP2

(A) Latent membrane protein 1 (LMP1). LMP1 is located within lipid rafts and associates with proteins that facilitate exosome secretion (CD63) and function (galectin 9). The carboxy terminal activating domains, CTAR1 and CTAR2, and the interacting TRAF molecules are denoted. The resultant effects on cellular signaling complexes with activation of kinases and distinct forms of NF-κB are indicated.

(B) Latent membrane protein 2 (LMP2). Schematic representation of specific domains including the SH2 Src kinase binding domain, the ITAM Syk binding site, and PPY binding site for Nedd4 ubiquitin ligases. Tyrosines are depicted as Y and prolines are depicted as P. The critical pathways that are activated through these interactions and the inhibition of the B cell receptor (BCR) are indicated.

Forty-four miRNAs arise from the introns of the BART transcripts (the BART miRNAs) and three miRNAs arise from around the BHRF1 ORF (Cai et al., 2006; Pfeffer et al., 2004). Some of the miRNAs may regulate viral mRNAs; however, most regulate host transcripts. Many potential targets have been identified with clear effects on apoptosis, tumor suppressors, and immune regulation. The spliced BART RNAs have also been shown to function as long non-coding RNAs (lncRNAs) with the potential for sponging and inactivating tumor suppressor miRNAs (Marquitz et al., 2015). Interestingly, EBV miRNAs can be secreted in exosomes and affect neighboring cells (Pegtel et al., 2010). Exosomes can be secreted during all forms of latency and potentially transfer viral oncoproteins, non-coding RNAs (ncRNAs), and key signaling molecules (Raab-Traub and Dittmer, 2017). This may modulate the tumor microenvironment.

Multiple other ncRNAs have been identified in EBV including a small nucleolar RNA encoded by the BART region and several potential circular RNAs from multiple regions of the genome (Moss et al., 2014; Ungerleider et al., 2019).

EBV REACTIVATION AND REPLICATION

Clinical importance of lytic EBV infection

The lytic form of EBV infection is required for production of infectious virions and is thus essential for the transmission of the virus from cell to cell and host to host. Lytic EBV replication can be inhibited by FDA-approved drugs, including ganciclovir, acyclovir, and foscarnet (Pagano et al., 2018). Chronic acyclovir therapy in healthy volunteers decreases the number of EBV-infected B cells (Hoshino et al., 2009), suggesting that EBV reactivation and replication may function to replenish the latently infected cell reservoir in the infected host. In oral hairy leukoplakia, lytic EBV infection of differentiated squamous epithelium produces white tongue lesions in immunocompromised hosts (Gewurz et al., 2021). Although a lytic-defective EBV mutant can transform B cells *in vitro* (Feederle et al., 2000), and EBV-positive malignancies are composed almost entirely of latently infected cells, there is growing evidence that lytic infection contributes to the early development of EBV-induced tumors. A lytic-defective EBV mutant missing the BZLF1 immediate-early gene (IE) is partially defective in inducing lymphomas in a

humanized mouse model (Ma et al., 2011), and lymphoblastoid B cell lines (LCLs) created with this mutant form tumors less efficiently than LCLs with wild-type EBV in severe combined immunodeficiency (SCID) mice (Hong et al., 2005a). In addition, lytically infected cells in tumors (although relatively rare) produce growth factors such as IL6 (Jones et al., 2007), angiogenesis factors such as VEGF (Hong et al., 2005b), and immunosuppressive factors such as IL10 (Mahot et al., 2003) that may promote proliferation and survival of latently infected tumors cells. Furthermore, abortive lytic infection may contribute to cellular gene mutations/alterations that drive EBV-positive tumors. In addition, EBV genomes containing variants of the viral BZLF1 promoter and EBER2 small nuclear RNA that cause increased lytic EBV infection (Bristol et al., 2018; Li et al., 2019) are highly over-represented in virus isolated from EBV-positive nasopharyngeal carcinomas in China versus virus isolated from healthy controls in the same region (Farrell and White, 2021)

Overview of lytic EBV replication

Lytic EBV genes are classified as IE, early or late lytic genes, with the names reflecting the temporal order in which they are expressed (Gewurz et al., 2012). EBV infection of normal differentiated oropharyngeal epithelial cells results in lytic infection without concomitant establishment of viral latency (Temple et al., 2014). On the other hand, EBV infection of B cells initially results in viral latency, although the virus can subsequently switch to the lytic form of infection (“lytically reactivate”) when cells undergo BCR activation or differentiate into plasma cells (Kenney and Mertz, 2014). Lytic reactivation is mediated by expression of the two viral IE lytic proteins, BZLF1 (a.k.a. Z, ZTA, ZEBRA) and BRLF1 (a.k.a. R, RTA) (Countryman and Miller, 1985; Deng et al., 2003; Flemington et al., 1992; Rooney et al., 1989; Zalani et al., 1996).

Z and R encode viral transcription factors that together activate expression of each of the early lytic EBV proteins required for the lytic form of EBV viral DNA replication, including the virally encoded DNA polymerase (BALF5) (Fixman et al., 1992; Kenney and Mertz, 2014), using the lytic origin of replication, OriLyt (Hammerschmidt and Sugden, 1988). Early lytic gene promoters contain *cis*–acting motifs that bind to Z and/or R (“ZREs” and “RREs,” respectively) and are transcriptionally activated when bound by the Z and/or R proteins (Kenney and Mertz, 2014). Transcription of late lytic EBV genes, which encode proteins required for virion assembly, occurs after viral genome replication and requires both a *cis*-acting viral replication origin and the virally encoded preinitiation complex (vPIC) that recruits RNA polymerase II (Aubry et al., 2014; Djavadian et al., 2016). The EBV early lytic SM protein is also required for transcription of a subset of late lytic genes, and this effect may be mediated through recruitment of the cellular transcription factor XPB to late promoters (Verma et al., 2020).

Lytic EBV DNA replication results in major reorganization of the host cell nucleus, with the viral replication compartments increasingly taking up most of the nuclear space (Chiu et al., 2013). Newly replicated viral genomes, which are unmethylated and have no chromatin, are linearized via the viral terminase complex, and then packaged into a pre-formed capsid particle (Gewurz et al., 2021). The nucleocapsid complex then exits the nucleus (in the process acquiring, and then losing, an envelope), and is deposited into the cytoplasm, where it becomes coated with viral proteins that form the “tegument” component of the virion particle (the region between the nucleocapsid and the virion envelope) (Gewurz et al., 2021). The particles then acquire a final envelope by budding into cis-Golgi and trans-Golgi networks, and vesicles containing mature virions are fused to the plasma membrane and are released by exocytosis (Gewurz et al., 2021.).

Regulation of lytic reactivation

The activity of the viral promoters driving Z and R expression (Zp and Rp, respectively) is primarily regulated by cellular transcription factors. Biologically important inducers of lytic EBV reactivation in B cells include B cell receptor activation and plasma cell differentiation (Kenney and Mertz, 2014; Laichalk and Thorley-Lawson, 2005). A variety of other stimuli, including hypoxia (via HIF-1 alpha), Hippo pathway signaling (via YAP/TAZ), inflammasome induction, and DNA damage can also induce lytic EBV reactivation (Burton et al., 2020; Kraus et al., 2017; Laichalk and Thorley-Lawson, 2005; Van Sciver et al., 2021b). In contrast, viral latency can be promoted by other cellular transcription factors including ZEB1/2, c-myc, KAP1, and IRF4 (Bristol et al., 2022; Guo et al., 2020a; Laichalk and Thorley-Lawson, 2005; Li et al., 2017). In differentiated oropharyngeal epithelial cells, EBV enters the lytic form of infection because the KLF4 and BLIMP1 cellular transcription factors collaboratively activate both Zp and Rp (Nawandar et al., 2015; Sixbey et al., 1984). In contrast, EBV enters latency in undifferentiated epithelial cells due to absence of KLF4/BLIMP1 expression and the presence of delta Np63, which inhibits Zp activity (Van Sciver et al., 2021a).

CpG DNA methylation and 5-hydroxymethylation differentially regulate the Z and R IE proteins

Increasing evidence suggests that CpG methylation status of the viral genome determines whether Z versus R initially activates early lytic gene transcription during viral reactivation. The Z protein, a homolog of Jun and Fos, preferentially binds to and transcriptionally activates CpG methylated ZREs in early lytic viral promoters (Bhende et al., 2004; Kalla et al., 2010). In contrast, although R can bind to methylated or unmethylated RREs in early lytic promoters, it preferentially activates promoters that are unmethylated (Wille et al., 2013). In contrast to CpG methylation, 5-hydroxymethylation of ZREs by cellular TET proteins inhibits Z binding and activation (Wille et al., 2015). EBV promotes DNA methylation of most lytic EBV genes in B cells through LMP1- and LMP2A-induced DNMT3A and DNMT1 expression (Guo et al., 2020b). However, Zp remain unmethylated, ensuring that Zp can be activated by specific cellular transcription factors associated with lytic reactivation. In EBV-infected telomerase-immortalized normal oral keratinocytes (NOKs), the EBV genome becomes much less methylated and only R expression, and not Z expression, induces lytic reactivation (Wille et al., 2015). R binding to RREs is not affected by 5′hydroxymethylation, and TET2 enhances R-mediated (but inhibits Z-mediated) lytic EBV reactivation in latently infected cells. Although these results suggest that transcription factors that activate Rp (rather than Zp) initiate lytic reactivation in normal keratinocytes, both Z and R

Table 2. EBV immune evasion proteins and ncRNAs

EBV gene	Expression	Function in immunity	Reference
BCRF1 (vIL-10)	lytic	Prevents B cells from being killed by NK cells. Impairs CD4+ T cell function.	Jochum et al., 2012
BDLF3	lytic	Inhibits CD1 presentation of MHC class I and II molecules.	Quinn et al., 2016
BGLF2	lytic	Binds Tyk2 and inhibits type I IFN.	Liu et al., 2020
BGLF5	lytic	Degrades TLR9.	van Gent et al., 2011
BHRF1	lytic	Degrades mitochondria and the MAVS protein, thereby reducing interferon signaling.	Vilmen et al., 2020
BILF1	lytic	Induces degradation of HLA-A and HLA-B molecules	Griffin et al., 2013
BNLF2A	lytic	Prevents MHC class I presentation of viral antigens to CD8+ T cells.	Jochum et al., 2012
BORF2	lytic	Inhibits APOBEC3B and innate immune responses.	Cheng et al., 2019
BPLF1	lytic	Targets TRIF, MyD88, TRAF6 to inhibit TLR and NF-κB activation.	Saito et al., 2013; van Gent et al., 2014
BZLF2 (gp42)	lytic	Prevents MHC class II antigen presentation to T cells	Spriggs et al., 1996
EBNA1	latent & lytic	Controls its own protein synthesis preventing EBNA1 peptides from being presented to T cells. Downregulates the expression of NKG2D ligands to prevent NK cell mediated killing of infected B cells.	Westhoff Smith et al., 2021; Yin et al., 2003
LMP1	latent & lytic	Suppresses TLR9 promoter.	Fathallah et al., 2010
LMP2A and 2B	latent	Target interferon receptors for degradation.	Shah et al., 2009
miR-BART6-3p	latent	Downregulates RIG-I and interferon response.	Lu et al., 2017
miR-BART15	latent	Latent Inhibits NLRP3 expression.	Haneklaus et al., 2012

are required for completion of lytic viral DNA replication and production of infectious virus regardless of cell type (Wille et al., 2013).

IMMUNE RESPONSES TO EBV

Innate immune responses

The host uses two levels of defense to counter infections with pathogens: the innate immune system (initial recognition of the infecting microbe) and the adaptive immune system (systemic recognition and long-term immune memory of the microbe). The innate immune response activates the adaptive response, leading to pathogen clearance. Innate immunity is the first line of defense against EBV. Innate immune sensors, also called pathogen recognition receptors (PRRs), recognize pathogen-associated molecular patterns (PAMPs) including DNA, RNA, and lipids present on viruses like EBV. PRRs include Toll-like receptors (TLRs), RIG-I like receptors (RLRs) and nucleotide-binding oligomerization domain, leucine rich repeat receptors (NLRs) (Kawai and Akira, 2008) and DNA sensors including cGAS and STING. cGAS signals through STING and is activated by viral DNA (Ma and Damania, 2016).

The PRRs important for EBV detection include TLRs, RLRs, and intracellular DNA sensors such as cGAS-STING and Absent in Melanoma-2 (AIM2)-like receptors (ALRs), including AIM2 and IFI16. Several TLRs have been shown to recognize EBV. TLR2 was shown to be activated by EBV and infection of primary human monocytes with EBV resulted in increased MCP-1 expression that was dependent on TLR2 expression (Gaudreault et al., 2007).

RIG-I has been described to sense EBERS through an RNA polymerase III-dependent process (Ablasser et al., 2009; Chiu et al., 2009; Duan et al., 2015; Samanta et al., 2006). Consistent with this observation, gastric cancer cells depleted for RIG-I have reduced inflammatory cytokine production during EBV viral reactivation (Chiang et al., 2018).Furthermore, the ALR, IFI16, can detect the EBV viral genome and is co-localized on the EBV genome in latently infected B cells. Depletion of IFI16 allowed for upregulation of EBV gene expression and viral replication in B cells (Pisano et al., 2017).

Innate immune cells including NK cells, invariant NK T (iNKT) cells, and gamma-delta T cells also recognize EBV (Chung et al., 2013a; Djaoud et al., 2017; Yuling et al., 2009). EBV infection results in NK cell expansion and these NK cells can

recognize lytically infected cells (Chijioke et al., 2016). Moreover, iNKT cells are thought to recognize newly EBV-infected B cells.

Adaptive immune responses

Adaptive immune responses recognize viral antigens and generate virus-specific immune responses that help to eliminate the virus from the infected host. Adaptive immunity involves the formation of immunologic memory so that future infection with the same virus can be curbed. Both B and T cells are part of the adaptive immune response to EBV.

EBV infection induces B cell activation resulting in increased production of IgM, IgG, and IgA. During the course of IM, antibodies against both latent and lytic viral antigens are detected. Neutralizing antibodies against gp350, gp42, and gH/gL can be found at varying times post-infection (Bu et al., 2019).

$CD8^+$ T cells are important during both acute and persistent EBV infection. $CD8^+$ T cells recognize EBV-infected cells because viral peptides are presented by major histocompatibility complex class I (MHC I) molecules on the surface of the infected cells (Pudney et al., 2005). It has been reported that almost half of the $CD8^+$ T cell population in newly infected people can be directed toward anti-EBV responses (Taylor et al., 2015).

IMMUNE EVASION BY EBV

Evasion of innate immunity

EBV has been reported to downregulate activation of several PRRs (Table 2). For example, EBV BPLF1 is a viral deubiquitinase that targets TRIF and MyD88 adaptor proteins as well as TRAF6 to downregulate both TRIF- and MyD88-dependent TLR activation and NF-κB activation (Saito et al., 2013; van Gent et al., 2014). Thus, BPLF1 reduces pro-inflammatory cytokine responses to EBV. During EBV lytic infection, the expression of TLR9 was found to be significantly decreased at both the RNA and protein levels through the function of EBV BGLF5, which degrades the TLR9 RNA transcript (van Gent et al., 2011). Moreover, EBV LMP-1 was also found to reduce TLR9 transcription through repression of the TLR9 promoter (Fathallah et al., 2010). Interestingly, EBV appears to utilize TLR7 for replication (Li et al., 2019). Some EBV EBER2 variants have been demonstrated to induce lytic EBV reactivation through the TLR7 signaling pathway, which is also important for reactivation of the related gammaherpesvirus, Kaposi sarcoma-associated herpesvirus (KSHV) (Gregory et al., 2009; Li et al., 2019).

EBV has also been shown to modulate RLR-mediated signaling through the mitochondrial adaptor protein, MAVS. EBV BHRF1 protein can promote mitochondrial fission leading to degradation of mitochondria and the MAVS protein, thereby reducing interferon signaling (Vilmen et al., 2020). Another viral protein, BPLF1, prevents TRIM25 from interacting with RIG-I through modulation of Tripartite motif-containing protein 25 (TRIM25) ubiquitination, thereby inhibiting the activation of RIG-I and preventing interferon (IFN) induction (Gupta et al., 2019). In addition to viral proteins, EBV viral miRNAs also target RLRs. EBV miR-BART6-3p was shown to downregulate both RIG-I and interferon (Lu et al., 2017). EBV miR-BART15 can also target the NLRP3 inflammasome. (Haneklaus et al., 2012).

EBV also targets DNA sensing pathways. EBV infection activates TRIM29, a protein that ubiquitinates and degrades the DNA sensor, STING, thereby resulting in decreased interferon responses in EBV-infected cells (Xing et al., 2017). It is postulated that APOBEC3B may convert cytosines to uracils in exposed single-stranded DNA replication intermediates of EBV, thereby inducing genomic mutations (Cheng et al., 2019). EBV BORF2 was demonstrated to inhibit the host DNA cytosine deaminase APOBEC3B (Cheng et al., 2019).

In addition to targeting specific PRR pathways as described above, EBV also targets multiple downstream components of the interferon signaling pathways including the interferon regulatory factors (IRFs), Janus kinase (JAK)-signal transducer and activator of transcription (STAT) signaling pathway, interferon-inducible genes (ISGs), as well as promoters of IFN alpha and beta. For example, both EBV LMP2A and LMP2B target interferon receptors for degradation (Shah et al., 2009), while BGLF2 interacts with Tyk2 to block interferon induction (Liu et al., 2020). Various mechanisms by which EBV modulates these central components of interferon signaling are reviewed in Lange et al. (2022).

Evasion of adaptive immunity

EBV is also a master at evading adaptive immune responses. EBV BDLF3 inhibits MHC class I and II presentation by ubiquitination-induced internalization (Quinn et al., 2016), whereas EBV BILF1 promotes the degradation of HLA-A and HLA-B (Griffin et al., 2013) (Table 2). Additionally, EBV BZLF2/gp42 functions to prevent MHC class II antigen presentation to T cells (Spriggs et al., 1996). Moreover, EBV BNLF2A inhibits the transporter associated with antigen processing (TAP), hindering peptide translocation from the cytoplasm to the ER(Jochum et al., 2012). Finally, EBV BPLF1 inhibits the proteasomal degradation of cytosolic proteins through its deubiquinating activity (Ernst et al., 2011). The EBV EBNA1 Gly-Ala repeats hinder protein synthesis of EBNA1, thereby preventing EBNA1 peptides from being presented to T cells (Yin et al., 2003). In a similar vein, LMP1 self-aggregation may prevent proteasome degradation and presentation to T cells (Smith et al., 2009), while EBV BCRF1 protein protects infected B cells from NK cell-mediated killing (Jochum et al., 2012). EBNA1 downregulates the expression of the NKG2D ligands, ULBP1 and ULBP5, and c-Myc in order to prevent NK cells from killing EBV-infected B cells (Westhoff Smith et al., 2021). EBV-encoded microRNAs also inhibit CD8 T cell recognition of EBV-infected B cells by down-regulating expression of the peptide transporter subunit TAP2 and the cytokine IL-12 (Albanese et al., 2016).

EBV oncogenesis

EBV-associated cancers can be stratified based on their latent gene expression programs (Table 1). Latency I was first identified in BL and subsequently found to also be present in gastric carcinoma. A second subset of EBV-positive cancers has moderate EBV viral gene expression and express the type II latency program. Examples of these EBV-positive malignancies include NPC and HL. A third subset of EBV-positive cancers occurs in immunocompromised or immunosuppressed individuals. Examples include HIV-associated lymphomas, PTLD, and lymphomas

that arise in individuals with genetic immunodeficiencies. These cancers display type III latency (Wen et al., 2021).

In all EBV-associated cancers, EBV is present in every tumor cell, the viral genome is typically clonal or oligoclonal, and at least one or more EBV latent viral gene(s) is expressed in the neoplastic cell. EBV-associated tumors express multiple latent genes and latent gene expression is thought to drive oncogenesis of EBV-positive malignancies. However, as described above there, are multiple mechanisms through which lytic viral genes also contribute to tumorigenesis.

EBV-ASSOCIATED DISEASES

IM

IM occurs in a subset of newly EBV-infected individuals, particularly in adolescents and young adults (Balfour et al., 2013a, 2013b). The major symptoms of IM are fever, fatigue, sore throat, and lymphadenopathy, with patients commonly having a high number of atypical lymphocytes. By 6 weeks post-infection, up to 50% of the memory B cells are infected with EBV (Hochberg et al., 2004), although the great majority of atypical lymphocytes are activated CD8 T lymphocytes directed against latent and lytic viral antigens, particularly the viral IE proteins and EBNA3 proteins (Rickinson et al., 2014). The "mono spot" test, used to diagnose acute EBV infection, is positive in up to 90% of adolescent and young adult IM patients (Gewurz et al., 2021). Specific serologic tests for EBV antigens (particularly anti-VCA IgM antibody) can also be used to diagnose acute EBV infection. Although patients with IM are often ill for several weeks, they almost always recover unless they have genetic defects that impair their immune response to EBV.

EBV initially infects oropharyngeal B cells where it enters different forms of viral latency, including the growth promoting form ("type III") that causes B cells to rapidly proliferate. The development of an effective CD8 T cell response eventually eliminates EBV-infected B cells with type III latency (Rickinson et al., 2014). Not surprisingly, anti-viral agents such as acyclovir that inhibit lytic, but not latent, EBV infection do not shorten the course or improve the symptoms of IM (Pagano et al., 2018).

The clinical symptoms of IM are likely mediated by an excessively strong cytotoxic T cell response to EBV-infected B cells, associated with increased levels of pro-inflammatory cytokines and chemokines. Proposed explanations for the milder illness in newly EBV-infected children versus older individuals include (1) an increased ability of NK T cells in children to recognize and kill EBV infected B cells, and (2) a higher inoculum of EBV in infected adolescents/young adults associated with "deep kissing" behavior (Balfour et al., 2013a). In addition, genetic risk factors, including HLA type, clearly contribute to the risk for developing IM (Rostgaard et al., 2014).

EBV-induced lymphoproliferative disease

EBV-induced lymphoproliferative disease (LPD) occurs when EBV-infected B cells contain the fully transforming form of latent EBV infection ("type III" latency), in which all nine latent EBV genes are expressed. Type III latency is sufficient to transform B cells *in vitro* but is also highly immunogenic, and thus LPD only occurs in highly immunocompromised patients, such as transplant patients (where it is referred to as PTLD) or patients with other disorders, including AIDS and inherited genetic mutations, affecting T cell or NK cell functions. Because EBV-encoded oncoproteins are the main "drivers" of LPD, newer therapies that directly target EBV infection per se, such as EBV-directed T cells, are increasingly used to treat LPD, in addition to conventional chemotherapy and reduction of immunosuppression (Heslop et al., 2010; Prockop et al., 2020). Therapeutic antibodies that deplete CD20- or CD19-expressing B cells are also particularly useful for treating and/or preventing EBV-induced LPD, since they not only kill lymphoma cells but also eliminate the normal memory B cell reservoir for EBV latency (Kim et al., 2019).

BLs

EBV-positive BLs most frequently occur in sub-Sahara Africa, where *Plasmodium falciparum* malaria infection is very common (Magrath, 2012). Greater than 90% of BLs in this region (referred to as "endemic" BLs) are EBV-infected and usually present as jaw tumors in children (Magrath, 2012). In contrast, BLs in other parts of the world ("sporadic" BLs) are usually EBV-negative. Both EBV-positive and EBV-negative BLs are driven by overexpression of the cellular c-myc oncogene, usually due to chromosomal translocations that place it under the control of one of the immunoglobulin gene enhancers. C-myc translocation likely occurs as an "accident" during the germinal center (GC) reaction in lymph nodes due to increased expression of the activation-induced cytosine deaminase (AID) enzyme. AID, which induces the DNA breaks required for immunoglobulin class-switching (Muramatsu et al., 2000), is expressed specifically in GC B cells and causes c-myc translocations to immunoglobulin loci as an "off-target" effect (Ramiro et al., 2004). *P. falciparum* infection has also been shown to contribute to the development of EBV-positive BLs by inducing polyclonal B cell activation (Simone et al., 2011) enhancing AID expression in GC B cells (Torgbor et al., 2014) and greatly increasing the number of EBV-infected B cells (Moormann et al., 2007; Njie et al., 2009; Simone et al., 2011). *P. falciparum* infection in children decreases the ability of T cells to control EBV infection (Moormann et al., 2007; Njie et al., 2009).

EBV infection is thought to promote BLs by suppressing apoptosis in cells over-expressing c-myc (Kennedy et al., 2003). Inhibition of apoptosis in human EBV-positive BLs is at least partially mediated by the virally encoded BART microRNAs, which decrease expression of apoptosis-inducing proteins such as caspase 3 (Vereide et al., 2014; Vereide and Sugden, 2011). Finally, EBV may also play a more direct role in promoting BLs by increasing expression of the AID protein (Kalchschmidt et al., 2016).

HLs

EBV is present in 30%–40% of classical HLs (Weiss et al., 1989; Wu et al., 1990). HLs are composed of malignant multinucleated Hodgkin and Reed-Sternberg (HRS) cells surrounded by non-malignant inflammatory cells (particularly CD4 T cells) that support the growth of the HRS cells (Mathas et al., 2016). Individuals who develop IM have an approximately 4-fold increased risk of subsequently developing EBV-positive (but not EBV-negative)

HL (Alexander et al., 2003; Hjalgrim et al., 2003). EBV-positive HLs have "type II" viral latency and express the LMP1 and LMP2A viral oncoproteins in the malignant HRS cells (Deacon et al., 1993). HRS cells, which are derived from post-GC B cells down-regulate B cell-specific markers and commonly contain cellular mutations that activate the NF-κB and JAK/STAT signaling pathways (Tiacci et al., 2018; Weniger and Küppers, 2021). Cellular mutations that activate the NF-κB pathway are much less common in EBV-positive versus EBV-negative HLs (Weniger and Küppers, 2021), presumably because both LMP1 and LMP2A can induce NF-κB signaling. Furthermore, approximately 25% of EBV-positive HLs contain crippling mutations in the BCR that would normally induce B cell death (Bräuninger et al., 2006), and LMP2A rescues survival of BCR-deficient B cells (Mancao and Hammerschmidt, 2007). Therefore, LMP2A functions as a surrogate BCR receptor in HRS cells. A naturally occurring EBV mutant (with a deleted EBNA2 gene that prevents type III latency) induces HL-like lymphomas with type II latency in a humanized mouse model (Li et al., 2020).

Diffuse large B cell lymphomas

Approximately 9% of diffuse large B cell lymphomas (DLBCLs), the most common type of non-HL, are EBV positive worldwide (Malpica et al., 2022). EBV + DLBCLs are now referred to as EBV + DLBCL NOS (not otherwise specified). Most EBV + positive DLBCLs support type II viral latency, although some display type III latency (particularly in the elderly and immunosuppressed) and rarely DLBCLs have type I latency (Bourbon et al., 2021). EBV infection is found in both the GC-type and "activated B cell" (ABC) type DLBCLs but is more common in ABC DLBCLs. EBV-positive DLBCLs more commonly show phenotypic activation of the JAK/STAT and NF-κB pathways compared to EBV-negative DLBCLs, consistent with the ability of LMP1 and LMP2A to activate these pathways (Ok et al., 2014). In addition, EBV-positive DLBCLs are less likely than EBV-negative DLBCLs to have mutations in the MYD88 and CD79B genes (Kataoka et al., 2019), suggesting that LMP2A and/or LMP1 expression compensates for these mutations. However, much larger studies comparing cellular gene mutations in EBV-positive versus EBV-negative DLBCLs need to be performed.

NK and T cell LPD

EBV infection can induce several different types of malignant and non-malignant diseases in T cells and NK cells, particularly in Asia and Central/South America. Malignancies associated with EBV infection of NK and T cells include extranodal NK/T cell lymphoma, systemic EBV-associated T cell lymphoma, and aggressive NK-cell leukemia (Cohen et al., 2020). Persistent EBV infection of NK cells and/or T cells can also cause chronic active EBV disease (CAEBV) and EBV-associated hemophagocytic lymphohistiocytosis (EBV-HLH) (Cohen et al., 2020; Kimura et al., 2003). These diseases have over-lapping epidemiologic, clinical, and genetic features, and are characterized by EBV infection of NK and/or T cells (usually with type II EBV latency) (Cohen et al., 2020; Kimura et al., 2003). EBV-induced HLH results from release of excessive levels of macrophage-activating cytokines (such as IFNγ and TNFα) from EBV-infected NK/T cells. Patients with EBV-HLH are at high risk for subsequently developing CAEBV and/or EBV-induced NK or T cell lymphomas. CAEBV is now considered to be an NK cell/T cell lymphoproliferative disease (Cohen et al., 2020; Kimura et al., 2003) and patients have an increased risk of developing NK or T cell lymphomas (NKTCLs) (Okuno et al., 2019). Thus, EBV-infected NK cells and T cells in CAEBV patients may be derived from a common EBV-infected progenitor lymphoid cell that can differentiate into either cell type. Interestingly, clonal deletions of the EBV genome that remove the BART microRNAs are found in 35% of CAEBV lymphocytes, and up to 43% of NKTCLs, but not in the EBV genomes of patients with IM (Okuno et al., 2019; Wongwiwat et al., 2022). Because BART microRNAs decrease expression of the lytic EBV proteins, BZLF1 and BRLF1 (Jung et al., 2014), loss of BARTs in EBV-infected NK/T cell diseases may be selected for in certain tumors/diseases to enhance expression of early lytic proteins. Currently, the most effective therapy for severe CAEBV is early hematopoietic stem cell (HSC) transplant (Dávila Saldaña et al., 2022).

NPC

The association of EBV with NPC was initially suggested by the unusually elevated antibody titers to specific viral antigens. The IgA titers that are indicative of NPC suggested that viral antigens were made within the tumor and induced a mucosal antibody response (Henle and Henle, 1976). EBV lytic antigens induce IgA antibodies that serve as specific markers for the detection, development, and re-occurrence of NPC. NPC develops with a high incidence of 20–50 cases per 100,000 in the endemic regions of Southern China and with elevated incidence in Mediterranean, Middle Eastern, and Inuit populations (Raab-Traub, 2015). Three subtypes of NPC are distinguished by their degree of differentiation and the virus is found in all three subtypes.

Importantly, EBV is present in the malignant epithelial cells in NPC and not in the lymphoid infiltrate. Analysis of EBV expression in NPC identified type II latency including transcription of LMP1 and LMP2 (Raab-Traub, 2015). Clonal viral DNA present in NPC indicates that the cells arose from a clonal origin (i.e., a single EBV-infected cell) (Raab-Traub and Flynn, 1986). A major contributing factor in the development of NPC is environmental exposures (including nutritional mutagens) that introduce preconditioning genetic changes in epithelial cells for NPC development and facilitate EBV latent infection. The essential contribution of EBV is evidenced by the universal retention of the EBV episome in NPC cells as well as expression of viral genes in every cell.

Multiple cellular tumor suppressor genes and oncogenes that are frequently mutated in carcinomas are not changed in NPC, likely reflecting the properties of EBV genes that regulate the expression or function of these proteins, eliminating the selection for genetic activation or inactivation. The p53 tumor suppressor is seldom mutated in NPC due to LMP1's inhibition of p53-induced apoptosis (Fries et al., 1996). Similarly, the induction of expression of EGFR is induced to high levels by LMP1. The activation of Akt by LMP2 eliminates the need for genetic inactivation of phosphatase and tensin homolog (PTEN) or mutational activation of β-catenin, which is detected at high levels in the nucleus in NPC (Morrison et al., 2004). Intriguingly, in a

subset of tumors, mutations have been identified within the NF-κB pathway including deletion of IkB-alpha, and mutations in TRAF3 and A20 that can negatively regulate activation (Chung et al., 2013b). These changes would lead to constitutive activation of this pathway in the absence of LMP1, confirming its importance to NPC pathogenesis. Subsequent work has determined that LMP1 expression and NF-κB activating mutations are mutually exclusive (Bruce et al., 2021). The strong endemic incidence of NPC has promoted many studies of NPC variants and variants in EBNA1, EBER2, the Z promoter, and the BALF2 gene have been identified.

Additionally, abundant expression of the BART miRNAs in NPC suggests that the miRNAs likely impact development and progression. In the C15 NPC xenograft, 57% of the total miRNAs were BART miRNAs, and in the C666 NPC xenograft, the BART miRNAs represented 40% of all miRNAs (Marquitz et al., 2014). The highly abundant BART miRNAs found in NPC tumors may reflect a selection for BART miRNA expression. Genes involved in apoptosis (e.g., Bim, PUMA, and TOMM22) have been shown to be targets of various BART miRNAs, in addition to genes involved in inhibition of T-cell responses to infected cells (Murer et al., 2019). It is likely that the specific targets may differ between cell lines and individual tumors; however, through the targeting of immune recognition, induction of cell invasion and metastasis, and promotion of tumorigenesis, the BART miRNAs are important factors in the development of NPC.

Gastric carcinoma

Gastric carcinoma is a major cancer with significant world-wide incidence with over one million cases per year and 800,000 deaths. Approximately 10% of all gastric cancer is linked to EBV and unlike NPC, EBV-associated gastric cancer does not have endemic patterns of incidence. However, EBV-associated gastric cancer is distinguished from other gastric cancer by a considerable lymphoid infiltrate (Strong et al., 2013). Gastric cancer is also unique in that the tumor genome is heavily methylated and the EBV-positive gastric cancer is distinguished by extremely high methylation termed CpG island Methylator Pheno-type (CIMP). It has been shown that chromatin structure and CpG methylation are major contributors to the maintenance of the EBV latency state and in gastric cancer, EBV expression is restricted to type I or II latency. EBV can induce hypermethylation to modify viral and cellular expression in epithelial cells (Stanland and Luftig, 2020). Sequence analyses have shown a lack of mutation in p53 and frequent mutations in PI3K as well as amplification of the PDL1/PDL2 locus. Because EBV-positive gastric cancer has a better prognosis compared to EBV-negative gastric cancer and is remarkably responsive to immune checkpoint inhibitors (Kim et al., 2018), screening all gastric cancers for the presence of EBV is probably warranted.

Autoimmune diseases associated with EBV

EBV infection has been linked to several autoimmune related disorders including SLE, Sjögren's syndrome, rheumatoid arthritis, and MS.

There is a strong correlation between EBV infection and SLE. Individuals with SLE display increased EBV antibody titers and viral DNA. Anti-EBNA1 antibodies appear to cross-react with SLE autoantigens, including Ro, Sm B/B′, and Sm D1 (Poole et al., 2006). Moreover, a study that examined transcription factor binding to the human genome revealed that the EBV EBNA2 protein binds to regulatory regions associated with SLE as well as other autoimmune disorders including MS, rheumatoid arthritis, etc. (Harley et al., 2018).

Similar to SLE patients, rheumatoid arthritis patients also display increased EBV viral DNA in their blood. These patients have a 2-fold increased risk of developing lymphoma (Callan, 2004), and EBV infection does not appear to be well controlled by their T cells. The numbers of EBV-infected B lymphocytes are also elevated (Balandraud and Roudier, 2018).

In MS, the myelin sheath of the CNS is under attack by autoreactive lymphocytes. Multiple epidemiological studies have associated EBV infection with MS and EBV-induced mononucleosis has been linked to an elevated risk of MS (Levin et al., 2010). A study of over 10 million military personnel in the US revealed an increased rate of EBV infection in MS patients compared to controls, and EBV-infected individuals were 32 times more likely to develop MS (Bjornevik et al., 2022). Furthermore, Neurofilament light chain (NfL) is a marker for neuroaxonal degeneration and NfL levels were significantly elevated in the sera of EBV-infected individuals with MS (Bjornevik et al., 2022). Another study reported the presence of cross-reactive cerebrospinal fluid (CSF) antibodies against EBV EBNA1 and human glial cell adhesion molecule (GlialCAM) in the CNS due to shared homology between the viral and human proteins (Lanz et al., 2022). Thus, molecular mimicry of viral and CNS myelin antigens is responsible for the pathological disease process and both anti-EBNA1 and anti-GlialCAM antibodies were found in MS patients. T cell responses against EBV proteins also cross-react with CNS proteins; for example, EBNA1-specific T cells in patients with MS cross-react with myelin antigens (Lunemann et al., 2008). Furthermore, in an autoimmune encephalomyelitis (EAE) mouse model of MS, injection of EBNA1 protein worsened disease (Lanz et al., 2022). Moreover, it has been reported that a significant number of brain-infiltrating B cells and plasma cells displayed EBV infection in 21 out of 22 postmortem MS brain specimens (Serafini et al., 2007). Post-mortem brains of MS patients also displayed CD8 cytotoxic T lymphocytes that recognize EBV latent and lytic proteins and interact with EBV-infected B cells (Serafini et al., 2019).

Conclusions

The 58 years since the discovery of EBV as a human tumor virus have been a remarkable foray into disease pathogenesis, growth control, molecular interactions, viral and cellular regulation, and environmental and genetic cofactors. These studies have shown that EBV can effectively thwart innate and adaptive immune responses, inhibit apoptotic and differentiation pathways, and enhance cell proliferation and angiogenesis (Figure 3). The outcome of infection in any specific cell can be quite variable with either replication or multiple states of non-replicative or "latent" infections. Importantly, this cycling of latency and reactivation is ongoing in all infected individuals increasing the likelihood that an unfortunate combination will occur; perhaps EBV infection of a GC cell in the process of class switching resulting in BL or infection of a mutant B cell, normally destined to die due to a non-functional BCR, that is instead rescued by EBV thereby

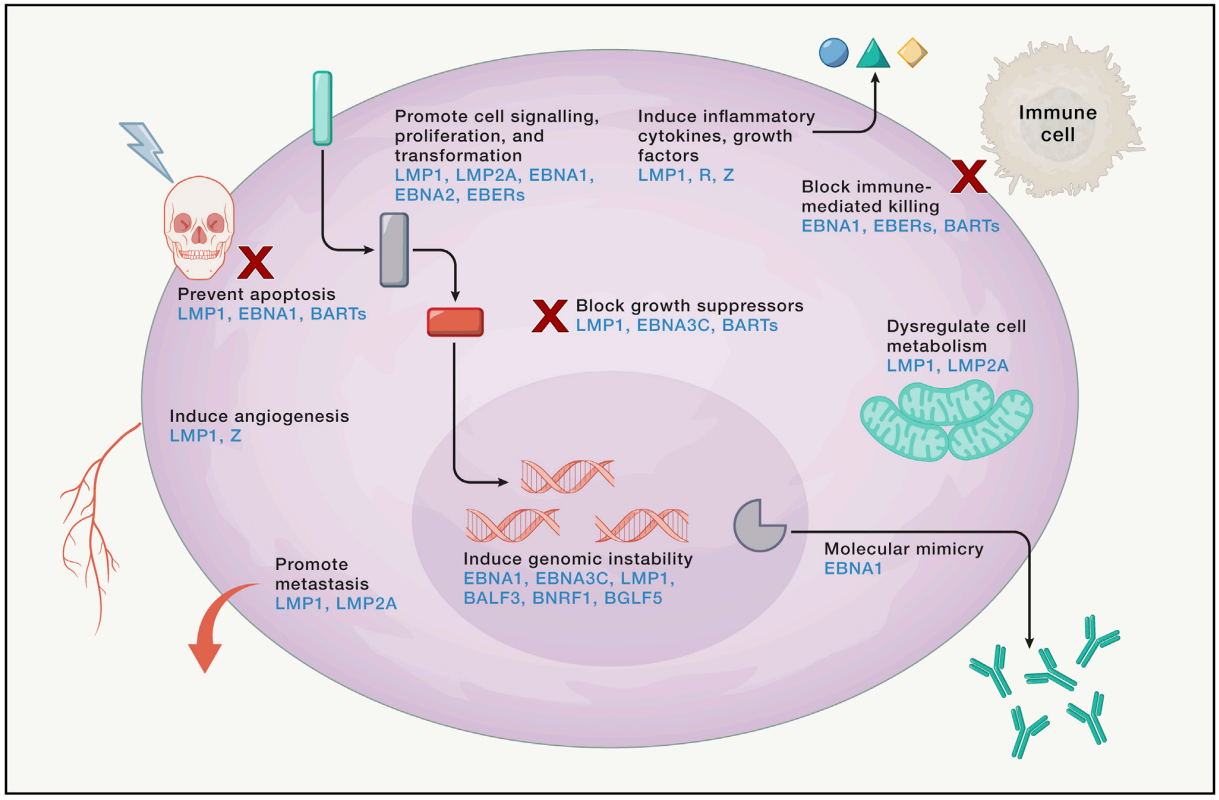

Figure 3. EBV modulation of the infected cell

EBV is a master regulator of the infected cell. EBV genes can inhibit apoptotic pathways (LMP1, EBNA1, and BARTs) and enhance cell proliferation and transformation pathways (LMP1, LMP2A, EBNA1, EBNA2, and EBERs), angiogenesis (LMP1 and Z), as well as promote metastasis (LMP1 and LMP2A). Several EBV genes also block growth suppressors (LMP1, EBNA3C, and BARTs). Multiple EBV proteins (EBNA1, EBNA3C, LMP1, BALF3, BNRF1, and BGLF5) have been demonstrated to induce genomic stability and dysregulate cell metabolic pathways (LMP1 and LMP2A). EBV genes can also inhibit host innate and adaptive immune responses (EBNA1, EBERs and BARTs) and induce inflammatory cytokine and growth factor expression (LMP1, Z, and R). Modulation of these pathways by EBV contribute to its oncogenic role in human malignancies. Additionally, EBV EBNA1 displays molecular mimicry with cellular proteins and contributes to EBV's role in autoimmune diseases, including multiple sclerosis.

resulting in HL. In southern China, the prevalence of a highly replicative variant increases the likelihood of infection of a nasopharyngeal epithelial cell with a set of mutations that activate cellular pathways that complement EBV-transforming proteins and allow the virus to establish viral latency. Alternatively, EBV may enter a cell and induce extensive cellular genome methylation such as found in gastric cancer and NPC, and can successfully establish infection and modulate cell proliferation through its abundant ncRNAs.

Additionally, both the initial immune response and the ongoing immune control can result in distinct outcomes and contribute to the development of IM or in devastating long-term effects of autoimmune diseases including MS. The complexity of the disease process in these many different outcomes of infection seems daunting given that this is a virus that infects most people in the world and establishes a lifelong infection. However, this complexity also offers many opportunities for therapeutic intervention. In addition to the highly successful EBV-specific cytotoxic T cell therapy, new drugs for specific targeting of critical pathways including NF-κB, PI3K, EGFR, and inhibitors of Src, Syk, or Btk kinases may be beneficial.

This panoply of devastating outcomes to EBV infection underscores the considerable need for an EBV vaccine, preferably one so effective that infection is completely blocked. An attenuated vaccine that still establishes a persistent infection such as the initial zoster vaccine would have the same possibilities for causing disease and may in fact be worse. Fortunately, there have been very encouraging results with several EBV vaccine prototypes. A phase I clinical trial based on a single glycoprotein, gp350, has just begun at NIH (NCT04645147). Perhaps likely to be more effective is a self-assembling nanoparticle composed of either 3 or 4 EBV glycoproteins gH/gL/gp42/gp350 used for entry into B cells and epithelial cells (Wei et al., 2022). This can induce significant humoral responses and blocked infection in humanized mouse models (Wei et al., 2022). The eventual development of a sterilizing vaccine will finally reveal the essential role of EBV in the multiple cancers that contain the virus and express its gene products in every cell. Importantly, it will also identify pathologies linked to continual immune anti-EBV hyperactivity such

as MS and potentially other diseases where traces of EBV have been shown. However, a vaccine that attenuates lytic EBV infection without preventing infection may still have significant ability to prevent IM and possibly also reduce the likelihood of EBV-induced cancers and autoimmune diseases.

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DECLARATION OF INTERESTS

The authors declare no competing interests.

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