Chapter 2
Epstein–Barr Virus: Pathogenesis and Host Immune Response

S. David Hudnall

Introduction

EBV is a human herpesvirus of the gamma-herpesvirus subfamily, genus *Lymphocryptovirus* with a ubiquitous worldwide distribution. Humans are the only known natural host for EBV, although Old World primate species harbor related lymphocryptoviruses [1–4]. EBV was first identified by electron microscopy of a biopsy of endemic African Burkitt lymphoma [5], and later identified as the cause of heterophile antibody positive infectious mononucleosis [6, 7]. In addition to endemic Burkitt lymphoma, EBV has been associated with a wide variety of other neoplasms, including non-Burkitt lymphoma, carcinoma, follicular dendritic cell sarcoma, and smooth muscle tumors [8–11]. In addition to malignant tumors, EBV is also associated with a variety of nonmalignant conditions including infectious mononucleosis, oral hairy leukoplakia [12], hemophagocytic syndrome [13], and chronic active EBV infection [14].

Permanently transformed B-cell lines harboring EBV can be obtained from the blood of patients with acute infectious mononucleosis, from Burkitt lymphoma tissue, and following in vitro EBV infection of normal peripheral blood B cells [15–17]. Much of our knowledge of the role of latent genes in B-cell transformation and lymphomagenesis has been obtained through the use of these readily available cell lines. Although only B cells appear to be efficiently infected and transformed in vitro, the host cell range for EBV in vivo includes T cells, plasma cells, epithelial cells, and mesenchymal cells [18]. The double-stranded EBV DNA genome sequenced from several isolates varies in size from 168 to 184 kbp and encodes for nearly 100 protein-coding genes [19–21]. The genome, flanked by tandem

S.D. Hudnall, M.D., F.C.A.P. (✉)
Department of Pathology and Laboratory Medicine, Director, Division of Hematopathology, Yale University School of Medicine, 310 Cedar Street, BML116B, New Haven, CT 06520-8023, USA
e-mail: david.hudnall@yale.edu

S.D. Hudnall (ed.), *Viruses and Human Cancer*, DOI 10.1007/978-1-4939-0870-7_2,
© Springer Science+Business Media New York 2014

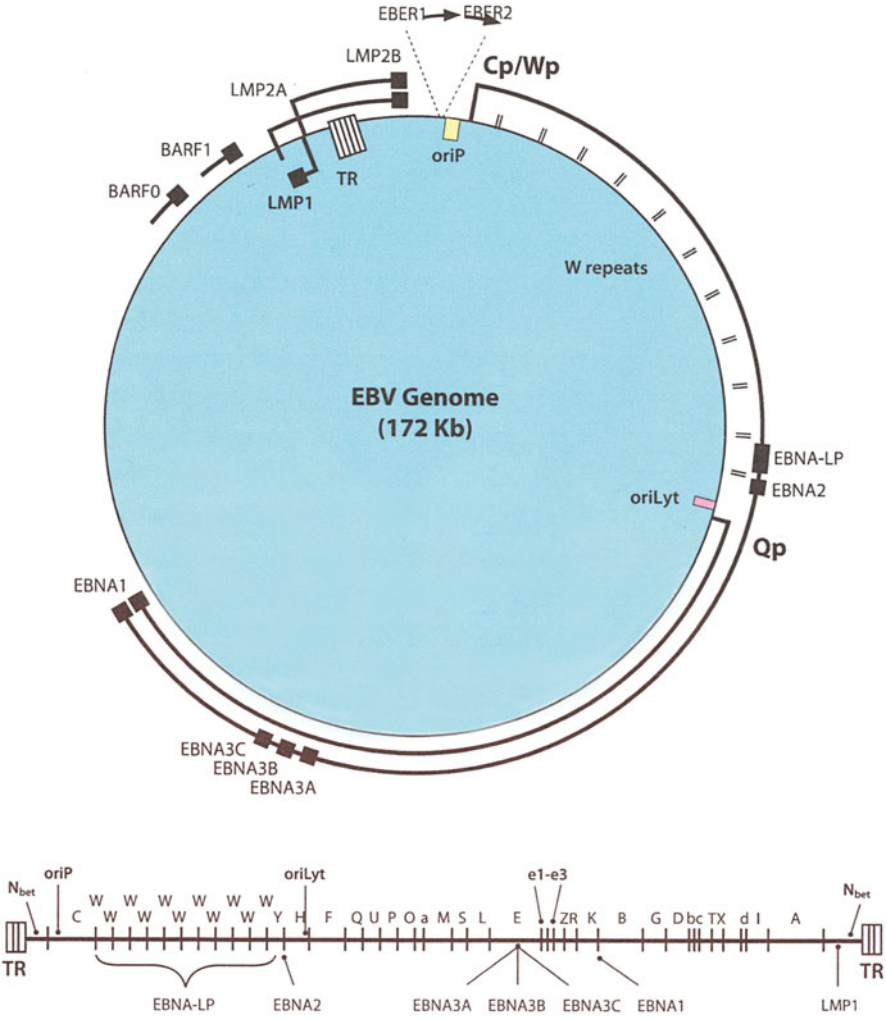


Fig. 2.1 Epstein–Barr virus genome (Adapted from Young & Rickinson [151])

approximately 500 base pair terminal repeat units [terminal repeats (TR)], contains 5 largely unique regions (from left to right UR1–5) alternating with 4 internal tandem repeat units (from left to right IR1–4) (Fig. 2.1). The EBV DNA genome, packaged in the virion as a linear molecule, undergoes circularization in the nucleus. The extra-chromosomal circular DNA molecule, known as the episome, forms by fusion within the terminal repeat regions [22]. In order to maintain the pool of latent-infected cells, episomal EBV undergoes host cell DNA polymerase-dependent duplication during the synthesis (S) phase of the cell cycle, thus ensuring partitioning of virus to all daughter cells [23]. In contrast, upon lytic activation, viral DNA polymerase-dependent replication yields several hundred copies of viral DNA per

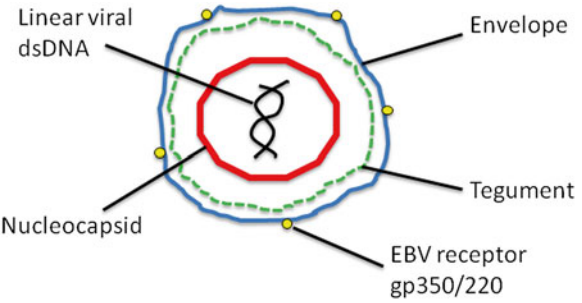


Fig. 2.2 Epstein–Barr virus structure

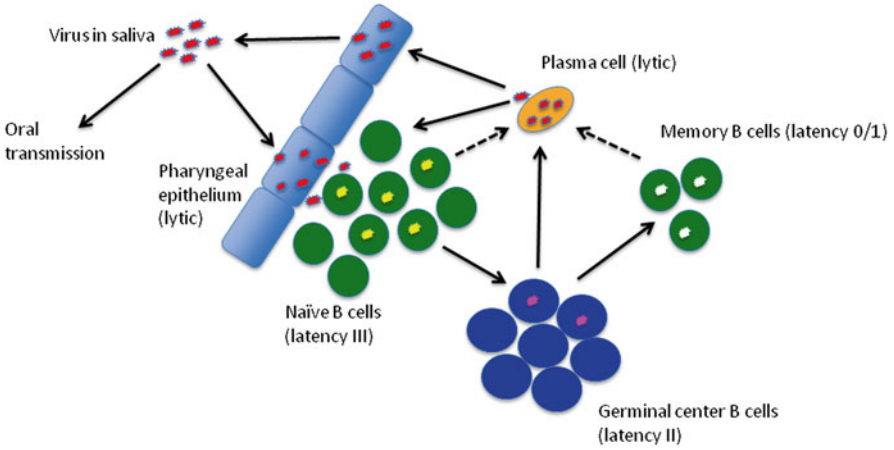


Fig. 2.3 Epstein–Barr virus life cycle

cell, each of which is encapsidated and enveloped for release as a mature virion [24–26] (Fig. 2.2).

Two EBV subtypes, EBV-1 and EBV-2, differ in genetic sequence, geographic distribution, and biologic properties [27, 28]. The genetic sequences primarily differ in the latent genes *EBER1*, *EBER2*, *EBNA2*, *EBNA3*, and *EBNA-LP*. In most parts of the world the EBV-1 strain predominates (80–90 %), with EBV-2 more often isolated in equatorial Africa, New Guinea, and from immunocompromised AIDS patients. Both strains can be recovered from the oropharynx of healthy persons from the developed world [27]. While EBV-1 isolates transform B cells in vitro with much greater efficiency than EBV-2 isolates [29], and are more commonly isolated from tumors [30], no clear difference in disease risk has been described.

Following initial exposure to infectious saliva, EBV likely undergoes a brief period of lytic replication in oral and nasal epithelium [31–33] (Fig. 2.3). Subsequent infection of naïve B cells within subjacent tonsillar lymphoid tissues leads to a brief "pre-latent" period of lytic and latent gene expression prior to epigenetic repression of viral genes [34]. This brief pre-latent period is marked by limited expression of a small set of lytic genes with regulatory function, excluding lytic genes essential

for DNA replication and virion assembly. It is likely that by promoting cell growth and inhibiting apoptosis, pre-latent lytic gene products, including BART miRNA, viral BCL-2 homologs, and BZLF1, contribute to the early survival of EBV-infected B cells [35]. Following epigenetic repression of the full complement of lytic genes and a subset of latent gene promoters [34, 36], rapid growth of latent-infected B cells is induced by expression of the full growth-promoting complement of latency genes, i.e., the latency III program [37]. Expression of the full complement of lytic and latent antigens by infected epithelial cells and B cells triggers a vigorous humoral and cellular immune response that leads to suppression of viral replication [38–40]. Latent-infected B cells persist by switching from the highly immunogenic latency III program to the less immunogenic latency II program, with virus gene expression restricted to three proteins, EBNA-1, LMP-1, and LMP-2A [41]. EBNA-1 maintains the viral genome [42], while LMP-1 and LMP-2A maintain cell growth while preventing apoptosis [43, 44]. The absence of EBNA-2-mediated transactivation allows for latency II B cells to adopt a germinal center B-cell phenotype and, in so doing, survive germinal center and/or extrafollicular proliferation and maturation into EBV-infected memory B cells [45, 46]. EBV-infected memory B cells persist by switching from the latency II program to the latency 0 program, with near-complete absence of viral gene expression, with only intermittent LMP-2a expression [45, 47, 48]. The EBV-positive resting memory B cells circulate in the blood, seeding lymphoid tissues throughout the body. Plasmacytic differentiation of EBV-positive memory B cells leads to end-stage viral replication [45, 49, 50]. Intermittent virus replication in oral and nasal tissues also leads to low-level shedding of virus in saliva and lifelong persistence of IgG anti-VCA antibody and EBV-specific cytotoxic T cells (CTL), more frequently directed against lytic antigens than latent antigens [51].

EBV Latent Genes

Given the importance of B-cell latency to virus persistence, a great deal of attention has been devoted to the classic latency genes, including six nuclear proteins (*EBNA-1*, *2*, *3A*, *3B*, *3C*, *LP*), three membrane proteins (*LMP-1*, *2A*, *2B*), and two small noncoding RNAs (*EBER-1*, *EBER-2*) (reviewed in [52]) (Table 2.1). Other EBV genes expressed during some forms of latency include *BART* (*BamH1* A fragment rightward transcripts) transcripts, *BHRF1* (*BamH1* R rightward reading frame 1) region transcripts, *BARF-0* (*BamH1* A fragment rightward reading frame 0) transcript, and *BARF-1* (*BamH1* A fragment rightward reading frame 1) protein. EBV infection of human peripheral blood B cells in vitro leads to the outgrowth of latent-infected transformed (so-called immortalized) lymphoblastoid B cells that express the full complement of latency genes (latency III). Using this in vitro model of EBV transformation, 4 of the 11 classic latent genes (*EBNA-2*, *EBNA-3A*, *EBNA-3C*, and *LMP-1*) have been demonstrated to be essential for in vitro B-cell transformation

Table 2.1 Epstein–Barr virus latency gene function

Gene	Function
EBER-1 and EBER-2	Block apoptosis and induce IL-10 production
EBNA-1	Maintains EBV episome copy number
EBNA-2	Enhances expression of viral and cellular genes
EBNA-3A	Limits EBNA-2 mediated transactivation
EBNA-3B	Blocks p53 and Rb activity
EBNA-3C	Limits EBNA-2 mediated transactivation
EBNA-LP	Cooperates with EBNA-2 in transactivation
LMP-1	Activates signaling pathways and blocks apoptosis
LMP-2A	Blocks lytic activation
LMP-2B	Enhances lytic activation
BART miRNA	Blocks regulators of proliferation and apoptosis
BHRF-1 miRNA	Inhibits latency III gene expression
BARF-0 RNA	Inhibits Notch signaling
BARF-1	Activates NF-kB and cyclin D1

[53–55]. While not essential for B-cell transformation, EBNA1 markedly enhances the rate of transformation [56]. Three patterns of EBV latency defined by differential expression of the latent genes have been described in infected B cells [57]—latency I with expression of EBNA1 only, latency II with expression of EBNA1 and LMP1, and latency III with expression of EBNA1, EBNA2, EBNA3 (A-C), EBNA-LP, LMP1, and LMP2. More recently a fourth form of latency termed latency 0 has been described in quiescent memory B cells, with EBV gene expression limited to intermittent expression of LMP-2a [58].

EBER-1 and EBER-2 RNA

Two small related noncoding *EBER* (EBV early RNA) genes (*EBER-1* and *EBER-2*) of uncertain function are highly expressed in all EBV-infected cells [59]. There are approximately 10^7 copies of *EBER* RNA in each infected cell, with an approximate *EBER-1* to *EBER-2* ratio of 10:1. EBER RNA is localized to the nucleus, bound to three cellular proteins La, L22, and EAP [60–64]. Interestingly, La protein, which functions in stabilization of tRNA, is a common autoantigen in both Sjögren syndrome and systemic lupus erythematosus [65]. While not essential for EBV-mediated B-cell transformation in vitro, the *EBERs* do enhance B-cell transformation in vitro [66] and contribute to growth of EBV-associated lymphoid and epithelial tumors [67, 68]. *EBER*-mediated effects that may contribute to tumor growth include up-regulation of IL-10 [69] and insulin-like growth factor (IGF-1) production [68], and inhibition of alpha interferon (IFNα)-mediated apoptosis [70, 71].

EBNA-1

In type I and type II latency, EBNA1 transcription is initiated by the BamH1Q latency promoter (*Qp*), while in latency III EBNA-1 transcription is initiated by the *Cp* and *Wp* promoters [72]. The DNA-binding EBNA-1 protein binds tightly to the viral latent origin of replication (*oriP*) region and tethers circular virus DNA molecules (episomes) to metaphase chromosomes, enabling episome duplication once per synthesis (S) cell cycle phase, and ensuring that all daughter cells remain EBV positive [73]. By maintaining a pool of infected cells within the host, EBNA-1 ensures lifelong asymptomatic viral persistence without the need for lytic production of infectious virus, an immune-stimulating event that threatens viral persistence. Furthermore, EBNA-1, by virtue of a glycine-alanine repeat domain that inhibits proteasome-mediated degradation and MHC class I-restricted presentation, evades immune recognition by CD8+ T cells even as it functions to ensure viral DNA persistence in latent-infected cells [74]. Although its primary function is in maintenance of latent virus, EBNA-1, unlike other EBNA, is also expressed during lytic activation via the alternative *Fp* promoter. While not essential for B-cell transformation, EBNA-1 nevertheless enhances outgrowth of EBV-transformed B cells in vitro, induces B-cell lymphoma in EBNA-1 transgenic mice [75], and protects EBV-negative Burkitt lymphoma cells from p53-mediated apoptosis. Also, EBNA-1 inhibition induces apoptosis of EBV-positive Burkitt lymphoma cells [76]. Thus, in addition to its primary role in maintaining latency, EBNA-1 likely contributes to latent persistence and EBV-related lymphoid neoplasia by inhibiting apoptosis of EBV-infected B cells.

EBNA-2

EBNA-2 is expressed during latency III and is essential for EBV-mediated B-cell transformation in vitro. EBNA-2 mimics the actions of a constitutively active Notch receptor by binding to the DNA-binding protein RBP-Jκ/CBF1 and transactivating several cellular and viral genes, including *CD21* (EBV receptor), *CD23*, *c-fgr*, *c-myc*, *LMP-1*, and *LMP-2* [77–82].

EBNA-3

The three *EBNA-3* genes (*3A*, *3B*, and *3C*) are located in tandem and transcribed under the control of the latency III promoters Cp and Wp. Unlike EBNA-3A and EBNA-3C, EBNA3B is not essential for in vitro EBV-mediated B-cell transformation [53]. All three EBNA-3 proteins repress EBNA-2 mediated transactivation by competing for binding to RBP-Jκ/CBF1 [83]. Overexpression of EBNA-3A in

lymphoblastoid cells leads to decreased c-myc expression and growth arrest. In spite of its nonessential role in the phenomenon of in vitro EBV-mediated B-cell transformation, EBNA-3B likely contributes to cell transformation by virtue of binding to p53 and RB [84]. In cooperation with EBNA-2, EBNA-3C up-regulates expression of the EBV receptor CD21 and LMP-1 [85–87], and cooperates with the *Ras* oncogene in the transformation of rodent cells [88].

EBNA-LP

EBNA-LP (EBNA leader protein), which is transcribed early at initiation of B-cell infection, cooperates with EBNA-2 in the transcriptional activation of several latent viral genes as well as cellular genes, including *c-myc* [89].

LMP-1

LMP-1 (latent membrane protein 1) is a transmembrane protein expressed in latency II and III that mimics the effect of a constitutively activated CD40-like TNF (tumor necrosis factor) receptor [90]. As such, LMP-1 expression leads to activation of several signaling pathways (NF-kB, Jak/Stat, MAP kinase, PI3K/Akt) that lead to cytokine production and inhibition of apoptosis [44, 91–97]. LMP-1, which is essential for lymphoblastoid B-cell transformation in vitro, induces transformation of rodent fibroblasts with tumor formation in nude mice [98]. *LMP1* transgenic mice develop epidermal hyperplasia, B-cell hyperplasia, and B-cell lymphomas [99]. These results indicate that *LMP1* is very likely a true viral oncogene.

LMP-2A and LMP-2B

The latent membrane protein LMP-2A, expressed in latency II and III, blocks lytic activation of EBV induced by cross-linking of surface IgM, CD19, or class II MHC [100, 101]. By preventing lytic activation of B cells, LMP-2A maintains latent persistence and long-term survival of EBV-infected B cells. By inhibiting NF-kB, LMP-2A inhibits proinflammatory cytokine production of EBV-infected B cells [102]. Furthermore, LMP-2A likely contributes to EBV-positive B-cell survival by inhibiting TGFβ-mediated apoptosis. In epithelial cells, LMP-2A induces proliferation in vitro and tumor formation in nude mice, and thus may contribute to the development of EBV-positive lymphocyte-rich carcinomas. The closely related EBV protein LMP-2B appears to function as an LMP-2A antagonist by enhancing the switch in EBV-infected B cells from latency to lytic activation [103].

BART RNA

EBV encodes for 29 miRNA transcripts from the *Bam*HI A (*BART*) and *Bam*HI R (*BHRF1*) regions [104]. *BART* transcripts (*Bam*H1 A rightward transcripts) are a small family of alternatively spliced miRNA transcripts expressed in both lymphoid and epithelial cells during all phases of EBV infection, and are particularly abundant in nasopharyngeal carcinoma [105–108]. At least six *BART* transcripts are present in EBV-positive lymphoid and epithelial cells [109]. During latency, *BART* transcripts appear to target a variety of regulators of cell proliferation and apoptosis [109, 110]. *BART miRNA* likely blocks apoptosis by inhibiting expression of the apoptotic protein caspase-3 [111]. While some *BART* transcripts encode putative open reading frames, no *BART*-encoded proteins have yet been detected in EBV-infected human cells [108].

BHRF1 RNA

BHRF1 (*Bam*H1 H rightward reading frame 1) region transcripts are produced during all phases of infection in both lymphoid and epithelial cells. *BHRF1* region miRNA transcripts suppress latent protein expression during latency type III, thereby enhancing cell survival by limiting immunogenicity [112]. BHRF1 miRNA also inhibits apoptosis and promotes cell proliferation of newly infected B cells [35].

BARF-0 RNA

The *BARF-0* (*Bam*H1 A rightward frame 0) gene encodes for an miRNA transcript in nasopharyngeal carcinoma that interferes with Notch signaling [113].

BARF-1

The *BARF-1* (*Bam*HI A rightward frame 1) gene encodes for a latent protein expressed in EBV-associated nasopharyngeal carcinoma and gastric carcinoma as well as in latent-infected B cells [114–116]. BARF-1 protein, with homology to human colony-stimulating factor 1 (CSF-1) receptor and ICAM-1, is capable of in vitro transformation of epithelial cells [117, 118]. By up-regulation of NF-kB and cyclin D1, and down-regulation of p21WAF1, BARF-1 may facilitate EBV-induced gastric cancer progression [119]. Thus, *BARF-1*, like *LMP-1*, appears to function as an oncogene, at least in EBV-associated carcinoma.

Patterns of Latent Gene Expression

Four distinct patterns of latent EBV gene expression have been described (Fig. 2.4). Type 0 latency, seen in memory B cells of healthy carriers, is characterized by EBV gene expression limited to noncoding *EBER RNA* and (transiently) *LMP-2A* protein [58]. Type I latency, typical of African Burkitt lymphoma and primary effusion lymphoma, is characterized by expression of *EBNA-1* protein, *EBER RNA*, and *BART-1 RNA* [57, 116]. Type II latency, typical of nasopharyngeal carcinoma, gastric carcinoma, T cell lymphoma, Hodgkin lymphoma, and latent-infected germinal center B cells [41] is characterized by expression of *EBER*, *EBNA-1*, *LMP-1*, and *LMP-2*. Type III latency, typical of in vitro transformed B cells and non-Hodgkin B-cell lymphoma, is characterized by expression of all classic latent genes including *EBER*, all 6 *EBNA* gene*s* (*1*, *2*, *3ABC*, *LP*), *LMP-1*, and *LMP-2* [57]. While ten latent EBV genes are active in EBV-transformed B cells, only a few are required for in vitro B-cell transformation (reviewed in [52]). *LMP-1* and *BARF-1* are the only latent genes that have clearly been shown to exhibit oncogenic activity [119, 120].

EBV Lytic Genes

The lytic viral genes encode for proteins involved in replication, cleavage, and packaging of viral DNA, and assembly of the capsid, tegument, and envelope. The temporal sequence of lytic gene expression begins with the immediate early genes, defined as viral genes whose transcription proceeds in the absence of protein synthesis. The two immediate early genes *BZLF1* and *BRLF1* encode for transcription factors that are required for lytic replication [121]. Binding of BZLF1 to the virus lytic origin of replication (*oriLyt*) initiates lytic virus replication, with participation by DNA-binding protein BALF2, DNA polymerase BALF5, DNA polymerase accessory protein BMRF1, and helicase-primase components BBLF2/3, BBLF4,

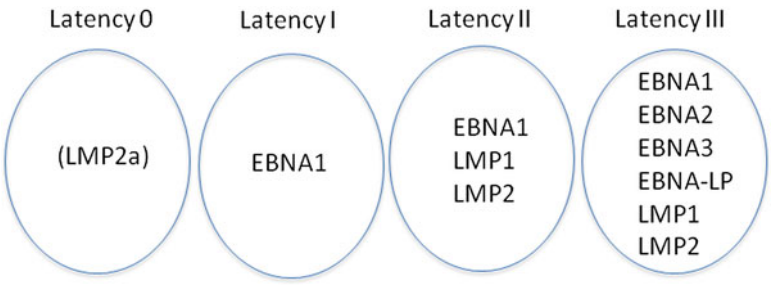


Fig. 2.4 Epstein–Barr virus latency patterns

and BSLF1 [26]. BZLF1-mediated transactivation of fully methylated lytic genes is preceded by epigenetic changes to target gene promoters [122]. BZLF1 also binds to a subset of cellular genes, inhibiting the expression of *NF-kB* and *p53* [123, 124]. The early lytic genes are those viral genes whose transcription proceeds in the absence of viral DNA synthesis. The early EBV gene *BSMLF1* (*SM*), which is essential for EBV replication, enhances the stability and export of intronless viral RNA to the cytoplasm [125, 126]. The early viral genes *BHRF1* and *BALF1* are *bcl-2* homologs that likely prevent apoptosis during the critical early phase of viral replication [127]. Other early genes include those responsible for DNA replication, including the viral DNA polymerase gene *BALF5*. Late lytic genes, defined as those viral genes for which transcription is dependent upon viral DNA synthesis, encode for proteins that make up the infectious virus particle, the virion, including nucleocapsid, tegument, and envelope glycoproteins. The most abundant envelope glycoprotein gp350/220 binds to the B-cell EBV receptor [complement C3d receptor (CR2), CD21] [128]. Some evidence suggests that $\alpha_5\beta_1$ integrin may serve as an alternative EBV receptor on epithelial cells [129].

Cellular Homology Genes

At least six EBV genes, *BALF1* (*bcl2*-like), *BARF-1* (*CSF1R* and *ICAM1*-like), *BCRF1* (*IL10*-like), *BDLF-2* (*cyclin B1*-like), *BHRF1* (*bcl2*-like), and *BZLF1* (*jun/fos*-like) share sequence homology with human genes [130–135]. These viral homolog genes may have been appropriated from the primate genome to provide a survival advantage to EBV-infected host cells, particularly during the early stages of primary infection.

Host Response to EBV Infection

Primary EBV infection triggers a humoral immune response, an innate NK cell response, and a CTL response [38, 40, 136, 137]. Shortly after infection, rapid rise and fall of IgM anti-VCA (virus capsid antigen) antibody is soon followed by IgG anti-VCA antibody that persists at a low titer for life. Antibodies to early antigens [diffuse (EA-D), methanol-resistant and restricted (EA-R), methanol-sensitive] as well as EBNA-2 rise and fall with convalescence, while antibodies to EBNA-1 develop only after convalescence and persist at a low titer for life (reviewed in [138]). Antibodies to the gp350 envelope protein, known as membrane antigen (MA), rise slowly during acute infection and persist after convalescence. The asymptomatic post-convalescent carrier state is characterized by persistent IgG antibody to VCA, MA, and EBNA-1. Virus reactivation occurring in immunocompromised virus carriers is marked by rising titers of IgG anti-VCA and anti-EA antibody, and accompanied by a rise in viral load in blood as detected by real-time

quantitative EBV PCR. In addition to virus-specific antibodies, patients with EBV-associated infectious mononucleosis rapidly and transiently develop heterophile antibodies, low titer IgM antibodies of unknown primary specificity that agglutinate heterologous (sheep, horse, cow) red blood cells [139]. Heterophile antibodies are both sensitive and specific for EBV-associated infectious mononucleosis since they are not usually seen in infectious mononucleosis syndromes associated with other infections. Patients with nasopharyngeal carcinoma specifically develop high titer IgA anti-VCA and EA-D antibodies [140].

The EBV-specific T cell response in acute primary infection (infectious mononucleosis) is dominated by CD8+ CTL with lytic antigen specificity, with a proportional increase in latent antigen specificity following recovery [141]. Lytic proteins targeted by EBV-specific CD8+ T cells are most often immediate early or early proteins rather than late proteins [142]. The CD8+ T-cell response to latent antigens is largely targeted to EBNA-3 proteins (3A, 3B, 3C) [143, 144]. The change in CD8+ T-cell antigen specificity likely reflects the biology of infection—acute primary infection initiated by a burst of lytic replication followed by immune suppression of lytic replication and establishment of a persistent pool of latent-infected B cells. In contrast to the CD8+ T-cell response, less is known about the CD4+ EBV-specific T-cell response during infectious mononucleosis. In a recent tetramer study of EBV epitope frequencies of CD4+ T cells in infectious mononucleosis, the most common epitopes included EBNA-2 and lytic antigens [145]. In studies of virus carriers, both lytic and latent antigen-specific CD4+ memory T cells have been detected in blood [146, 147]. In one study EBV-specific CD4+ T cells were almost entirely lytic antigen-specific [148]. In contrast to CD8+ T cells, lytic antigens targeted by cytotoxic CD4+ T cells include not only immediate early and early lytic proteins but also late lytic proteins [145]. In contrast to the dominance of EBNA-3 latent antigen specificity of CD8+ T cells, CD4+ T cells are more often directed against EBNA-1, EBNA-2, and EBNA-3C [149, 150].

References

1. Lee YS, Tanaka A, Lau RY, Nonoyama M, Rabin H. Comparative studies of herpesvirus papio (baboon herpesvirus) DNA and Epstein-Barr virus DNA. J Gen Virol. 1980;51:245–53.
2. Böcker JF, Tiedemann KH, Bornkamm GW, zur Hausen H. Characterization of an EBV-like virus from African green monkey lymphoblasts. Virology. 1980;101:291–5.
3. Kieff E, Dambaugh T, Heller M, et al. The biology and chemistry of Epstein-Barr virus. J Infect Dis. 1982;146:506–17.
4. Lapin BA, Timanovskaya VV, Yakovleva LA. Herpesvirus HVMA: a new representative in the group of the EBV-like B-lymphotropic herpesviruses of primates. Haematol Blood Transfus. 1985;29:312–3.
5. Epstein MA, Achong BG, Barr YM. Virus particles in cultured lymphoblasts from Burkitt's lymphoma. Lancet. 1964;1:702–3.
6. Diehl V, Henle G, Henle W, Kohn G. Demonstration of a herpes group virus in cultures of peripheral leukocytes from patients with infectious mononucleosis. J Virol. 1968;2:663–9.

7. Henle G, Henle W, Diehl V. Relation of Burkitt's tumor-associated herpes-type virus to infectious mononucleosis. Proc Natl Acad Sci U S A. 1968;59:94–101.
8. Weiss L, Movahed L. In situ demonstration of Epstein-Barr viral genomes in viral-associated B cell lymphoproliferations. Am J Pathol. 1989;134:651–9.
9. Su IJ, Hsieh HC. Clinicopathological spectrum of Epstein-Barr virus-associated T cell malignancies. Leuk Lymphoma. 1992;7:47–53.
10. Shimazaki K, Ohshima K, Haraoka S, Suzumiya J, Nakamura N, Kikuchi M. Accessory cell tumour: a clinicopathological study of 16 aggressive tumours containing EBV-positive Hodgkin and Reed-Sternberg-like giant cells. Histopathology. 2002;40:12–21.
11. Purgina B, Rao UN, Miettinen M, Pantanowitz L. AIDS-related EBV-associated smooth muscle tumors: a review of 64 published cases. Patholog Res Int. 2011;2011:561548.
12. Schiødt M, Greenspan D, Daniels TE, Greenspan JS. Clinical and histologic spectrum of oral hairy leukoplakia. Oral Surg Oral Med Oral Pathol. 1987;64:716–20.
13. Okano M, Gross TG. Epstein-Barr virus-associated hemophagocytic syndrome and fatal infectious mononucleosis. Am J Hematol. 1996;53:111–5.
14. Kimura H. Pathogenesis of chronic active Epstein-Barr virus infection: is this an infectious disease, lymphoproliferative disorder, or immunodeficiency? Rev Med Virol. 2006;16:251–61.
15. Epstein MA, Achong BG, Pope JH. Virus in cultured lymphoblasts from a New Guinea Burkitt lymphoma. Br Med J. 1967;2:290–1.
16. Pope JH, Achong BG, Epstein MA, Biddulph J. Burkitt lymphoma in New Guinea: establishment of a line of lymphoblasts in vitro and description of their fine structure. J Natl Cancer Inst. 1967;39:933–45.
17. Pope JH, Scott W, Moss DJ. Human lymphoid cell transformation by Epstein-Barr virus. Nat New Biol. 1973;246:140–1.
18. Hudnall SD, Ge Y, Wei L, Yang NP, Wang HQ, Chen T. Distribution and phenotype of Epstein-Barr virus-infected cells in human pharyngeal tonsils. Mod Pathol. 2005;18:519–27.
19. Bornkamm G, Delius H, Zimber U, Hudewentz J, Epstein M. Comparison of Epstein-Barr virus strains of different origin by analysis of the viral DNAs. J Virol. 1980;35:603–18.
20. Baer R, Bankier AT, Biggin MD, et al. DNA sequence and expression of the B95-8 Epstein-Barr virus genome. Nature. 1984;310:207–11.
21. Lin Z, Wang X, Strong MJ, et al. Whole-genome sequencing of the Akata and Mutu Epstein-Barr virus strains. J Virol. 2013;87:1172–82.
22. Alfieri C, Birkenbach M, Kieff E. Early events in Epstein-Barr virus infection of human B lymphocytes. Virology. 1991;181:595–608.
23. Yates JL, Guan N. Epstein-Barr virus-derived plasmids replicate only once per cell cycle and are not amplified after entry into cells. J Virol. 1991;65:483–8.
24. Sato H, Takimoto T, Tanaka S, Tanaka J, Raab-Traub N. Concatameric replication of Epstein-Barr virus: structure of the termini in virus-producer and newly transformed cell lines. J Virol. 1990;64:5295–300.
25. Tsurumi T, Fujita M, Kudoh A. Latent and lytic Epstein-Barr virus replication strategies. Rev Med Virol. 2005;15:3–15.
26. Hammerschmidt W, Sugden B. Replication of Epstein-Barr viral DNA. Cold Spring Harb Perspect Biol. 2013;5:a013029.
27. Sixbey JW, Shirley P, Chesney PJ, Buntin DM, Resnick L. Detection of a second widespread strain of Epstein-Barr virus. Lancet. 1989;2:761–5.
28. Apolloni A, Sculley TB. Detection of A-type and B-type Epstein-Barr virus in throat washings and lymphocytes. Virology. 1994;202:978–81.
29. Sculley TB, Apolloni A, Hurren L, Moss DJ, Cooper DA. Coinfection with A- and B-type Epstein-Barr virus in human immunodeficiency virus-positive subjects. J Infect Dis. 1990;162:643–8.
30. Peh SC, Kim LH, Poppema S. Frequent presence of subtype A virus in Epstein-Barr virus-associated malignancies. Pathology. 2002;34:446–50.
31. Walling DM, Flaitz CM, Nichols CM, Hudnall SD, Adler-Storthz K. Persistent productive Epstein-Barr virus replication in normal epithelial cells in vivo. J Infect Dis. 2001;184:1499–507.

32. Herrmann K, Frangou P, Middeldorp J, Niedobitek G. Epstein-Barr virus replication in tongue epithelial cells. J Gen Virol. 2002;83:2995–8.
33. Frangou P, Buettner M, Niedobitek G. Epstein-Barr virus (EBV) infection in epithelial cells in vivo: rare detection of EBV replication in tongue mucosa but not in salivary glands. J Infect Dis. 2005;191:238–42.
34. Kalla M, Schmeinck A, Bergbauer M, Pich D, Hammerschmidt W. AP-1 homolog BZLF1 of Epstein-Barr virus has two essential functions dependent on the epigenetic state of the viral genome. Proc Natl Acad Sci U S A. 2010;107:850–5.
35. Seto E, Moosmann A, Grömminger S, Walz N, Grundhoff A, Hammerschmidt W. Micro RNAs of Epstein-Barr virus promote cell cycle progression and prevent apoptosis of primary human B cells. PLoS Pathog. 2010;6:e1001063.
36. Tierney R, Kirby H, Nagra J, Desmond J, Bell A, Rickinson A. Methylation of transcription factor binding sites in the Epstein-Barr virus latent cycle promoter Wp coincides with promoter down-regulation during virus-induced B-cell transformation. J Virol. 2000;74: 10468–79.
37. Tierney RJ, Steven N, Young LS, Rickinson AB. Epstein-Barr virus latency in blood mononuclear cells: analysis of viral gene transcription during primary infection and in the carrier state. J Virol. 1994;68:7374–85.
38. Hislop AD, Taylor GS, Sauce D, Rickinson AB. Cellular responses to viral infection in humans: lessons from Epstein-Barr virus. Annu Rev Immunol. 2007;25:587–617.
39. De Paschale M, Clerici P. Serological diagnosis of Epstein-Barr virus infection: problems and solutions. World J Virol. 2012;1:31–43.
40. Chijioke O, Azzi T, Nadal D, Münz C. Innate immune responses against Epstein Barr virus infection. J Leukoc Biol. 2013;94(6):1185–90.
41. Babcock GJ, Hochberg D, Thorley-Lawson AD. The expression pattern of Epstein-Barr virus latent genes in vivo is dependent upon the differentiation stage of the infected B cell. Immunity. 2000;13:497–506.
42. Yates JL, Warren N, Sugden B. Stable replication of plasmids derived from Epstein-Barr virus in various mammalian cells. Nature. 1985;313:812–5.
43. Caldwell RG, Wilson JB, Anderson SJ, Longnecker R. Epstein-Barr virus LMP2A drives B cell development and survival in the absence of normal B cell receptor signals. Immunity. 1998;9:405–11.
44. Gires O, Kohlhuber F, Kilger E, et al. Latent membrane protein 1 of Epstein-Barr virus interacts with JAK3 and activates STAT proteins. EMBO J. 1999;18:3064–73.
45. Babcock GJ, Decker LL, Volk M, Thorley-Lawson DA. EBV persistence in memory B cells in vivo. Immunity. 1998;9:395–404.
46. Babcock GJ, Thorley-Lawson DA. Tonsillar memory B cells, latently infected with Epstein-Barr virus, express the restricted pattern of latent genes previously found only in Epstein-Barr virus-associated tumors. Proc Natl Acad Sci U S A. 2000;97:12250–5.
47. Thorley-Lawson DA, Babcock GJ. A model for persistent infection with Epstein-Barr virus: the stealth virus of human B cells. Life Sci. 1999;65:1433–53.
48. Hochberg D, Middeldorp JM, Catalina M, Sullivan JL, Luzuriaga K, Thorley-Lawson DA. Demonstration of the Burkitt's lymphoma Epstein-Barr virus phenotype in dividing latently infected memory cells in vivo. Proc Natl Acad Sci U S A. 2004;101:239–44.
49. Anagnostopoulos I, Hummel M, Kreschel C, Stein H. Morphology, immunophenotype, and distribution of latently and/or productively Epstein-Barr virus-infected cells in acute infectious mononucleosis: implications for the interindividual infection route of Epstein-Barr virus. Blood. 1995;85:744–50.
50. Laichalk LL, Thorley-Lawson DA. Terminal differentiation into plasma cells initiates the replicative cycle of Epstein-Barr virus in vivo. J Virol. 2005;79:1296–307.
51. Tan LC, Gudgeon N, Annels NE, et al. A re-evaluation of the frequency of CD8+ T cells specific for EBV in healthy virus carriers. J Immunol. 1999;162:1827–35.
52. Kieff E, Rickinson A. Epstein–Barr virus and its replication, Fields Virolog. Lippincott Williams & Wilkins. 2007.

53. Tomkinson B, Robertson E, Kieff E. Epstein-Barr virus nuclear proteins EBNA-3A and EBNA-3C are essential for B-lymphocyte growth transformation. J Virol. 1993;67: 2014–25.
54. Wang F, Kikutani H, Tsang SF, Kishimoto T, Kieff E. Epstein-Barr virus nuclear protein 2 transactivates a cis-acting CD23 DNA element. J Virol. 1991;65:4101–6.
55. Kaye KM, Izumi KM, Kieff E. Epstein-Barr virus latent membrane protein 1 is essential for B-lymphocyte growth transformation. Proc Natl Acad Sci U S A. 1993;90:9150–4.
56. Humme S, Reisbach G, Feederle R, et al. The EBV nuclear antigen 1 (EBNA1) enhances B cell immortalization several thousandfold. Proc Natl Acad Sci U S A. 2003;100:10989–94.
57. Rowe M, Lear AL, Croom-Carter D, Davies AH, Rickinson AB. Three pathways of Epstein-Barr virus gene activation from EBNA1-positive latency in B lymphocytes. J Virol. 1992;66:122–31.
58. Miyashita EM, Yang B, Babcock GJ, Thorley-Lawson DA. Identification of the site of Epstein-Barr virus persistence in vivo as a resting B cell. J Virol. 1997;71:4882–91.
59. Glickman JN, Howe JG, Steitz JA. Structural analyses of EBER1 and EBER2 ribonucleoprotein particles present in Epstein-Barr virus-infected cells. J Virol. 1988;62:902–11.
60. Houmani JL, Davis CI, Ruf IK. Growth-promoting properties of Epstein-Barr virus EBER-1 RNA correlate with ribosomal protein L22 binding. J Virol. 2009;83:9844–53.
61. Toczyski DP, Steitz JA. EAP, a highly conserved cellular protein associated with Epstein-Barr virus small RNAs (EBERs). EMBO J. 1991;10:459–66.
62. Toczyski DP, Matera AG, Ward DC, Steitz JA. The Epstein-Barr virus (EBV) small RNA EBER1 binds and relocalizes ribosomal protein L22 in EBV-infected human B lymphocytes. Proc Natl Acad Sci U S A. 1994;91:3463–7.
63. Lerner MR, Andrews NC, Miller G, Steitz JA. Two small RNAs encoded by Epstein-Barr virus and complexed with protein are precipitated by antibodies from patients with systemic lupus erythematosus. Proc Natl Acad Sci U S A. 1981;78:805–9.
64. Fok V, Friend K, Steitz JA. Epstein-Barr virus noncoding RNAs are confined to the nucleus, whereas their partner, the human La protein, undergoes nucleocytoplasmic shuttling. J Cell Biol. 2006;173:319–25.
65. Harley JB, Scofield RH, Reichlin M. Anti-Ro in Sjögren's syndrome and systemic lupus erythematosus. Rheum Dis Clin North Am. 1992;18:337–58.
66. Yajima M, Kanda T, Takada K. Critical role of Epstein-Barr Virus (EBV)-encoded RNA in efficient EBV-induced B-lymphocyte growth transformation. J Virol. 2005;79:4298–307.
67. Iwakiri D, Eizuru Y, Tokunaga M, Takada K. Autocrine growth of Epstein-Barr virus-positive gastric carcinoma cells mediated by an Epstein-Barr virus-encoded small RNA. Cancer Res. 2003;63:7062–7.
68. Iwakiri D, Sheen TS, Chen JY, Huang DP, Takada K. Epstein-Barr virus-encoded small RNA induces insulin-like growth factor 1 and supports growth of nasopharyngeal carcinoma-derived cell lines. Oncogene. 2005;24:1767–73.
69. Samanta M, Iwakiri D, Takada K. Epstein-Barr virus-encoded small RNA induces IL-10 through RIG-I-mediated IRF-3 signaling. Oncogene. 2008;27:4150–60.
70. Nanbo A, Inoue K, Adachi-Takasawa K, Takada K. Epstein-Barr virus RNA confers resistance to interferon-alpha-induced apoptosis in Burkitt's lymphoma. EMBO J. 2002;21: 954–65.
71. Ruf IK, Lackey KA, Warudkar S, Sample JT. Protection from interferon-induced apoptosis by Epstein-Barr virus small RNAs is not mediated by inhibition of PKR. J Virol. 2005;79:14562–9.
72. Zetterberg H, Stenglein M, Jansson A, Ricksten A, Rymo L. Relative levels of EBNA1 gene transcripts from the C/W, F and Q promoters in Epstein-Barr virus-transformed lymphoid cells in latent and lytic stages of infection. J Gen Virol. 1999;80(Pt 2):457–66.
73. Middleton T, Sugden B. Retention of plasmid DNA in mammalian cells is enhanced by binding of the Epstein-Barr virus replication protein EBNA1. J Virol. 1994;68:4067–71.
74. Levitskaya J, Sharipo A, Leonchiks A, Ciechanover A, Masucci MG. Inhibition of ubiquitin/proteasome-dependent protein degradation by the Gly-Ala repeat domain of the Epstein-Barr virus nuclear antigen 1. Proc Natl Acad Sci U S A. 1997;94:12616–21.

75. Wilson JB, Bell JL, Levine AJ. Expression of Epstein-Barr virus nuclear antigen-1 induces B cell neoplasia in transgenic mice. EMBO J. 1996;15:3117–26.
76. Kennedy G, Komano J, Sugden B. Epstein-Barr virus provides a survival factor to Burkitt's lymphomas. Proc Natl Acad Sci U S A. 2003;100:14269–74.
77. Abbot SD, Rowe M, Cadwallader K, et al. Epstein-Barr virus nuclear antigen 2 induces expression of the virus-encoded latent membrane protein. J Virol. 1990;64:2126–34.
78. Ling PD, Hsieh JJ, Ruf IK, Rawlins DR, Hayward SD. EBNA-2 upregulation of Epstein-Barr virus latency promoters and the cellular CD23 promoter utilizes a common targeting intermediate, CBF1. J Virol. 1994;68:5375–83.
79. Kaiser C, Laux G, Eick D, Jochner N, Bornkamm GW, Kempkes B. The proto-oncogene c-myc is a direct target gene of Epstein-Barr virus nuclear antigen 2. J Virol. 1999;73:4481–4.
80. Wang L, Grossman SR, Kieff E. Epstein-Barr virus nuclear protein 2 interacts with p300, CBP, and PCAF histone acetyltransferases in activation of the LMP1 promoter. Proc Natl Acad Sci U S A. 2000;97:430–5.
81. Strobl LJ, Höfelmayr H, Marschall G, Brielmeier M, Bornkamm GW, Zimber-Strobl U. Activated Notch1 modulates gene expression in B cells similarly to Epstein-Barr viral nuclear antigen 2. J Virol. 2000;74:1727–35.
82. Gordadze AV, Peng R, Tan J, et al. Notch1IC partially replaces EBNA2 function in B cells immortalized by Epstein-Barr virus. J Virol. 2001;75:5899–912.
83. Robertson ES, Lin J, Kieff E. The amino-terminal domains of Epstein-Barr virus nuclear proteins 3A, 3B, and 3C interact with RBPJ(kappa). J Virol. 1996;70:3068–74.
84. Szekely L, Selivanova G, Magnusson KP, Klein G, Wiman KG. EBNA-5, an Epstein-Barr virus-encoded nuclear antigen, binds to the retinoblastoma and p53 proteins. Proc Natl Acad Sci U S A. 1993;90:5455–9.
85. Wang F, Tsang SF, Kurilla MG, Cohen JI, Kieff E. Epstein-Barr virus nuclear antigen 2 transactivates latent membrane protein LMP1. J Virol. 1990;64:3407–16.
86. Allday MJ, Crawford DH, Thomas JA. Epstein-Barr virus (EBV) nuclear antigen 6 induces expression of the EBV latent membrane protein and an activated phenotype in Raji cells. J Gen Virol. 1993;74(Pt 3):361–9.
87. Lin J, Johannsen E, Robertson E, Kieff E. Epstein-Barr virus nuclear antigen 3C putative repression domain mediates coactivation of the LMP1 promoter with EBNA-2. J Virol. 2002;76:232–42.
88. Parker GA, Crook T, Bain M, Sara EA, Farrell PJ, Allday MJ. Epstein-Barr virus nuclear antigen (EBNA)3C is an immortalizing oncoprotein with similar properties to adenovirus E1A and papillomavirus E7. Oncogene. 1996;13:2541–9.
89. Harada S, Kieff E. Epstein-Barr virus nuclear protein LP stimulates EBNA-2 acidic domain-mediated transcriptional activation. J Virol. 1997;71:6611–8.
90. Izumi KM, Kaye KM, Kieff ED. The Epstein-Barr virus LMP1 amino acid sequence that engages tumor necrosis factor receptor associated factors is critical for primary B lymphocyte growth transformation. Proc Natl Acad Sci U S A. 1997;94:1447–52.
91. Dawson CW, Tramountanis G, Eliopoulos AG, Young LS. Epstein-Barr virus latent membrane protein 1 (LMP1) activates the phosphatidylinositol 3-kinase/Akt pathway to promote cell survival and induce actin filament remodeling. J Biol Chem. 2003;278:3694–704.
92. Young LS, Murray PG. Epstein-Barr virus and oncogenesis: from latent genes to tumours. Oncogene. 2003;22:5108–21.
93. Dirmeier U, Hoffmann R, Kilger E, et al. Latent membrane protein 1 of Epstein-Barr virus coordinately regulates proliferation with control of apoptosis. Oncogene. 2005;24:1711–7.
94. Dudziak D, Kieser A, Dirmeier U, et al. Latent membrane protein 1 of Epstein-Barr virus induces CD83 by the NF-kappaB signaling pathway. J Virol. 2003;77:8290–8.
95. Laherty CD, Hu HM, Opipari AW, Wang F, Dixit VM. The Epstein-Barr virus LMP1 gene product induces A20 zinc finger protein expression by activating nuclear factor kappa B. J Biol Chem. 1992;267:24157–60.
96. Eliopoulos AG, Gallagher NJ, Blake SM, Dawson CW, Young LS. Activation of the p38 mitogen-activated protein kinase pathway by Epstein-Barr virus-encoded latent membrane

protein 1 coregulates interleukin-6 and interleukin-8 production. J Biol Chem. 1999;274: 16085–96.
97. Eliopoulos AG, Blake SM, Floettmann JE, Rowe M, Young LS. Epstein-Barr virus-encoded latent membrane protein 1 activates the JNK pathway through its extreme C terminus via a mechanism involving TRADD and TRAF2. J Virol. 1999;73:1023–35.
98. Wilson JB, Weinberg W, Johnson R, Yuspa S, Levine AJ. Expression of the BNLF-1 oncogene of Epstein-Barr virus in the skin of transgenic mice induces hyperplasia and aberrant expression of keratin 6. Cell. 1990;61:1315–27.
99. Kulwichit W, Edwards RH, Davenport EM, Baskar JF, Godfrey V, Raab-Traub N. Expression of the Epstein-Barr virus latent membrane protein 1 induces B cell lymphoma in transgenic mice. Proc Natl Acad Sci U S A. 1998;95:11963–8.
100. Miller CL, Lee JH, Kieff E, Longnecker R. An integral membrane protein (LMP2) blocks reactivation of Epstein-Barr virus from latency following surface immunoglobulin crosslinking. Proc Natl Acad Sci U S A. 1994;91:772–6.
101. Dykstra ML, Longnecker R, Pierce SK. Epstein-Barr virus coopts lipid rafts to block the signaling and antigen transport functions of the BCR. Immunity. 2001;14:57–67.
102. Stewart S, Dawson CW, Takada K, et al. Epstein-Barr virus-encoded LMP2A regulates viral and cellular gene expression by modulation of the NF-kappaB transcription factor pathway. Proc Natl Acad Sci U S A. 2004;101:15730–5.
103. Rechsteiner MP, Berger C, Zauner L, et al. Latent membrane protein 2B regulates susceptibility to induction of lytic Epstein-Barr virus infection. J Virol. 2008;82:1739–47.
104. Edwards RH, Marquitz AR, Raab-Traub N. Epstein-Barr virus BART microRNAs are produced from a large intron prior to splicing. J Virol. 2008;82:9094–106.
105. Brooks LA, Lear AL, Young LS, Rickinson AB. Transcripts from the Epstein-Barr virus BamHI A fragment are detectable in all three forms of virus latency. J Virol. 1993;67: 3182–90.
106. Gilligan KJ, Rajadurai P, Lin JC, et al. Expression of the Epstein-Barr virus BamHI A fragment in nasopharyngeal carcinoma: evidence for a viral protein expressed in vivo. J Virol. 1991;65:6252–9.
107. Thornburg NJ, Kusano S, Raab-Traub N. Identification of Epstein-Barr virus RK-BARF0-interacting proteins and characterization of expression pattern. J Virol. 2004;78:12848–56.
108. Marquitz AR, Raab-Traub N. The role of miRNAs and EBV BARTs in NPC. Semin Cancer Biol. 2012;22:166–72.
109. Yamamoto T, Iwatsuki K. Diversity of Epstein-Barr virus BamHI-A rightward transcripts and their expression patterns in lytic and latent infections. J Med Microbiol. 2012;61:1445–53.
110. Pfeffer S, Zavolan M, Grässer FA, et al. Identification of virus-encoded microRNAs. Science. 2004;304:734–6.
111. Vereide DT, Seto E, Chiu YF, et al. Epstein-Barr virus maintains lymphomas via its miRNAs. Oncogene. 2014;33(10):1258–64.
112. Feederle R, Linnstaedt SD, Bannert H, et al. A viral microRNA cluster strongly potentiates the transforming properties of a human herpesvirus. PLoS Pathog. 2011;7:e1001294.
113. Kusano S, Raab-Traub N. An Epstein-Barr virus protein interacts with Notch. J Virol. 2001;75:384–95.
114. Decaussin G, Sbih-Lammali F, de Turenne-Tessier M, Bouguermouh A, Ooka T. Expression of BARF1 gene encoded by Epstein-Barr virus in nasopharyngeal carcinoma biopsies. Cancer Res. 2000;60:5584–8.
115. zur Hausen A, Brink AA, Craanen ME, Middeldorp JM, Meijer CJ, van den Brule AJ. Unique transcription pattern of Epstein-Barr virus (EBV) in EBV-carrying gastric adenocarcinomas: expression of the transforming BARF1 gene. Cancer Res. 2000;60:2745–8.
116. Fiorini S, Ooka T. Secretion of Epstein-Barr virus-encoded BARF1 oncoprotein from latently infected B cells. Virol J. 2008;5:70.
117. Guo X, Sheng W, Zhang Y. [Malignant transformation of monkey kidney epithelial cell induced by EBV BARF1 gene and TPA]. Zhonghua Shi Yan He Lin Chuang Bing Du Xue Za Zhi. 2001;15:321–3.

118. Hoebe EK, Hutajulu SH, van Beek J, et al. Purified hexameric Epstein-Barr virus-encoded BARF1 protein for measuring anti-BARF1 antibody responses in nasopharyngeal carcinoma patients. Clin Vaccine Immunol. 2011;18:298–304.
119. Chang MS, Kim DH, Roh JK, et al. Epstein-Barr virus-encoded BARF1 promotes proliferation of gastric carcinoma cells through regulation of NF-κB. J Virol. 2013;87:10515–23.
120. Klein E, Teramoto N, Gogolák P, Nagy N, Björkholm M. LMP-1, the Epstein-Barr virus-encoded oncogene with a B cell activating mechanism similar to CD40. Immunol Lett. 1999;68:147–54.
121. Feederle R, Kost M, Baumann M, et al. The Epstein-Barr virus lytic program is controlled by the co-operative functions of two transactivators. EMBO J. 2000;19:3080–9.
122. Woellmer A, Arteaga-Salas JM, Hammerschmidt W. BZLF1 governs CpG-methylated chromatin of Epstein-Barr Virus reversing epigenetic repression. PLoS Pathog. 2012;8: e1002902.
123. Zhang Q, Gutsch D, Kenney S. Functional and physical interaction between p53 and BZLF1: implications for Epstein-Barr virus latency. Mol Cell Biol. 1994;14:1929–38.
124. Dreyfus DH, Nagasawa M, Pratt JC, Kelleher CA, Gelfand EW. Inactivation of NF-kappaB by EBV BZLF-1-encoded ZEBRA protein in human T cells. J Immunol. 1999;163: 6261–8.
125. Cook ID, Shanahan F, Farrell PJ. Epstein-Barr virus SM protein. Virology. 1994;205: 217–27.
126. Ruvolo V, Gupta AK, Swaminathan S. Epstein-Barr virus SM protein interacts with mRNA in vivo and mediates a gene-specific increase in cytoplasmic mRNA. J Virol. 2001;75: 6033–41.
127. Altmann M, Hammerschmidt W. Epstein-Barr virus provides a new paradigm: a requirement for the immediate inhibition of apoptosis. PLoS Biol. 2005;3:e404.
128. Fingeroth JD, Weis JJ, Tedder TF, Strominger JL, Biro PA, Fearon DT. Epstein-Barr virus receptor of human B lymphocytes is the C3d receptor CR2. Proc Natl Acad Sci U S A. 1984;81:4510–4.
129. Tugizov SM, Berline JW, Palefsky JM. Epstein-Barr virus infection of polarized tongue and nasopharyngeal epithelial cells. Nat Med. 2003;9:307–14.
130. Pearson GR, Luka J, Petti L, et al. Identification of an Epstein-Barr virus early gene encoding a second component of the restricted early antigen complex. Virology. 1987;160:151–61.
131. Hayes DP, Brink AA, Vervoort MB, Middeldorp JM, Meijer CJ, van den Brule AJ. Expression of Epstein-Barr virus (EBV) transcripts encoding homologues to important human proteins in diverse EBV associated diseases. Mol Pathol. 1999;52:97–103.
132. Strockbine LD, Cohen JI, Farrah T, et al. The Epstein-Barr virus BARF1 gene encodes a novel, soluble colony-stimulating factor-1 receptor. J Virol. 1998;72:4015–21.
133. Packham G, Economou A, Rooney CM, Rowe DT, Farrell PJ. Structure and function of the Epstein-Barr virus BZLF1 protein. J Virol. 1990;64:2110–6.
134. Marshall WL, Yim C, Gustafson E, et al. Epstein-Barr virus encodes a novel homolog of the bcl-2 oncogene that inhibits apoptosis and associates with Bax and Bak. J Virol. 1999;73:5181–5.
135. Niiro H, Otsuka T, Abe M, et al. Epstein-Barr virus BCRF1 gene product (viral interleukin 10) inhibits superoxide anion production by human monocytes. Lymphokine Cytokine Res. 1992;11:209–14.
136. Khanna R, Burrows SR. Role of cytotoxic T lymphocytes in Epstein-Barr virus-associated diseases. Annu Rev Microbiol. 2000;54:19–48.
137. Landais E, Saulquin X, Houssaint E. The human T cell immune response to Epstein-Barr virus. Int J Dev Biol. 2005;49:285–92.
138. Rickinson A, Kieff E. Epstein Barr Virus, Fields Virology. Lippincott Williams & Wilkins. 2007.
139. Evans AS, Niederman JC. EBV-IgA and new heterophile antibody tests in diagnosis of infectious mononucleosis. Am J Clin Pathol. 1982;77:555–60.
140. Henle G, Henle W. Epstein-Barr virus-specific IgA serum antibodies as an outstanding feature of nasopharyngeal carcinoma. Int J Cancer. 1976;17:1–7.

141. Hislop AD, Annels NE, Gudgeon NH, Leese AM, Rickinson AB. Epitope-specific evolution of human CD8(+) T cell responses from primary to persistent phases of Epstein-Barr virus infection. J Exp Med. 2002;195:893–905.
142. Steven NM, Annels NE, Kumar A, Leese AM, Kurilla MG, Rickinson AB. Immediate early and early lytic cycle proteins are frequent targets of the Epstein-Barr virus-induced cytotoxic T cell response. J Exp Med. 1997;185:1605–17.
143. Steven NM, Leese AM, Annels NE, Lee SP, Rickinson AB. Epitope focusing in the primary cytotoxic T cell response to Epstein-Barr virus and its relationship to T cell memory. J Exp Med. 1996;184:1801–13.
144. Callan MF, Tan L, Annels N, et al. Direct visualization of antigen-specific CD8+ T cells during the primary immune response to Epstein-Barr virus in vivo. J Exp Med. 1998;187: 1395–402.
145. Long HM, Chagoury OL, Leese AM, et al. MHC II tetramers visualize human CD4+ T cell responses to Epstein-Barr virus infection and demonstrate atypical kinetics of the nuclear antigen EBNA1 response. J Exp Med. 2013;210:933–49.
146. Amyes E, Hatton C, Montamat-Sicotte D, et al. Characterization of the CD4+ T cell response to Epstein-Barr virus during primary and persistent infection. J Exp Med. 2003;198:903–11.
147. Woodberry T, Suscovich TJ, Henry LM, et al. Differential targeting and shifts in the immunodominance of Epstein-Barr virus-specific CD8 and CD4 T cell responses during acute and persistent infection. J Infect Dis. 2005;192:1513–24.
148. Mautner J, Bornkamm GW. The role of virus-specific CD4+ T cells in the control of Epstein-Barr virus infection. Eur J Cell Biol. 2012;91:31–5.
149. Leen A, Meij P, Redchenko I, et al. Differential immunogenicity of Epstein-Barr virus latent-cycle proteins for human CD4(+) T-helper 1 responses. J Virol. 2001;75:8649–59.
150. Long HM, Haigh TA, Gudgeon NH, et al. CD4+ T-cell responses to Epstein-Barr virus (EBV) latent-cycle antigens and the recognition of EBV-transformed lymphoblastoid cell lines. J Virol. 2005;79:4896–907.
151. Young LS, Rickinson AB. Epstein-Barr virus: 40 years on. Nature Reviews Cancer 2004; 4:757–768.

http://www.springer.com/978-1-4939-0869-1

Viruses and Human Cancer
Hudnall, S.D. (Ed.)
2014, XI, 386 p. 95 illus., 74 illus. in color., Hardcover
ISBN: 978-1-4939-0869-1