



# Epstein–Barr virus latent genes

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## REVIEW

# Epstein–Barr virus latent genes

Myung-Soo Kang<sup>1,2</sup> and Elliott Kieff<sup>3</sup>

Latent Epstein–Barr virus (EBV) infection has a substantial role in causing many human disorders. The persistence of these viral genomes in all malignant cells, yet with the expression of limited latent genes, is consistent with the notion that EBV latent genes are important for malignant cell growth. While the EBV-encoded nuclear antigen-1 (EBNA-1) and latent membrane protein-2A (LMP-2A) are critical, the EBNA-leader proteins, EBNA-2, EBNA-3A, EBNA-3C and LMP-1, are individually essential for *in vitro* transformation of primary B cells to lymphoblastoid cell lines. EBV-encoded RNAs and EBNA-3Bs are dispensable. In this review, the roles of EBV latent genes are summarized.

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## INTRODUCTION

A physician by name Burkitt was the first to describe a unique lymphoma. Epstein and Barr then discovered virus particles in cultured lymphoblasts from Burkitt's lymphoma (BL) in 1964.<sup>1</sup> The Epstein–Barr virus (EBV) infection is ubiquitous in adult humans.<sup>2–4</sup> Higher titer of EBV antibody was evident in BL, lymphoproliferative diseases (LPDs), Hodgkin's lymphoma (HL), endemic nasopharyngeal carcinoma (NPC) and infectious mononucleosis.<sup>5–13</sup> EBV primarily infects the human oropharynx epithelial cells, and then replicates and spreads to B cells, resulting in latent infection in B cells, epithelial cells and natural killer/T cells after extensive host T-cell immune surveillance.<sup>14–33</sup> Latent EBV infection substantially causes many human malignancies. In immunocompetent people, EBV likely causes ~20% of BL in the developed world, almost all African BL, 50% of HL, 10% gastric carcinomas (GCs), almost all endemic NPC, certain fractions of diffuse large B-cell lymphoma and T-cell lymphoma, multiple sclerosis and systemic lupus erythematosus (SLE).<sup>5–13,34,35</sup> In the absence of normal T-cell immune responses, EBV-infected B-lymphocyte proliferations can cause LPD, similar to posttransplant LPD. The persistence of EBV genomes in all cells of these malignancies, even in people with otherwise normal immune responses, is consistent with the notion that EBV genomes are important for malignant cell growth.

## EBV LATENT INFECTION

Latent EBV genomes express five EBV-encoded nuclear antigens (EBNA) and two latent membrane proteins (LMPs), namely EBV-encoded small RNA (EBER) and non-transcribed BART (*Bam*HI-A region rightward transcript) RNAs. Primary EBV infection establishes typically three distinct latent infection statuses from the initial infection as a non-integrated episome: latency types III, II and I depending on the viral gene expression pattern.<sup>27–33</sup> Actively proliferating (post-transplantation) lymphoproliferative diseases and *in vitro* EBV infection-mediated establishment of the lymphoblastoid cell line (LCL) show type III latency, in which most latent genes are expressed (EBER1/2 RNA, EBNA-leader protein (EBNA-LP), EBNA-2, EBNA-3ABC, EBNA-1, LMP-2A/B, LMP-1 protein, BART RNA). HL and NPC display type II latency (EBER1/2 RNA, EBNA-1, LMP-2A/B, LMP-1 (type IIa) or EBNA-2 (type IIb), BART RNA) and BL shows type I latency (EBER1/2 RNA, EBNA-1, LMP-2A/B, BART RNA). Although EBNA-1 and LMP-2A play a critical role, EBNA-LP, EBNA-2, EBNA-3A, EBNA-3C and LMP-1 are individually essential for *in vitro* transformation of primary B cells to LCLs.<sup>36–38</sup>

The EBV's role in cell growth is most evident in latency III EBV-associated posttransplant LPD, as EBNA-2, EBNA-LP, EBNA-3A and EBNA-3C in latency III infection coordinately upregulate cMyc expression and cell proliferation, and EBV LMP-1 enhances cell survival.<sup>39–58</sup> Furthermore, EBV's role is also evident in latency II-infected HL and NPC, where LMP-1

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**Table 1 Roles of EBV-encoded latent genes**

<i>Latent genes</i>	<i>Roles</i>
<i>EBNA-1</i>	Sequence-specific DNA-binding protein to EBV element; sequence-nonspecific chromosome association protein; transactivator of viral latent genes and host genes; responsible for episome replication, segregation and persistence of viral genome; involved in p53 degradation and oncogenesis
<i>EBNA-LP</i>	Transcriptional coactivator of EBNA-2-dependent viral and cellular gene transcription; primarily indirectly associates with host DNA sites located at or near the transcriptional start; associates with cellular transcriptional (co)factors and EBNA-2; dismisses repressor complex from promoter or enhancer sites; is essential for EBV-mediated B-cell transformation
<i>EBNA-2</i>	Together with EBNA-LP cooperatively activates viral and cellular gene transcription for transformation; primarily indirectly associates with host DNA sites located at the enhancer or intergenic region; associates with cellular transcriptional (co)factors and EBNA-LP; is critical for EBV-mediated B-cell transformation
<i>EBNA-3A</i>	A coactivator of EBNA-2, EBNA-3A and EBNA-3C associations with RBPJ inhibit RBPJ recruitments to DNA; downregulate cMyc transcription and block EBNA-2 activation effects; and induce CDKN2 and chemokines. Induces G1 arrests, which is essential for EBV-mediated B-cell transformation
<i>EBNA-3B</i>	A coactivator of EBNA-2; dispensable for B-cell transformation; viral tumor suppressor; and upregulates CXCL10. EBNA-3B-knockout induces DLBCL-like tumors
<i>EBNA-3C</i>	Coactivates with EBNA-2 host <i>CXCR4</i> and <i>CXCL12</i> genes; induces CDKN2, chemokines and aurora kinase B; mediates RB degradation; attenuates H2AX expression and overcomes EBV-infection-mediated DNA damage response; promotes cell proliferation; induces G1 arrests; essential for EBV-mediated B-cell transformation
<i>LMP-1</i>	Mimics the constitutively active form of CD40, a major EBV-encoded oncogene; activates NF- $\kappa$ B, JNK and p38 pathways; is critical for EBV-mediated B-cell transformation, a major EBV-encoded oncogene; activates NF- $\kappa$ B, JNK and p38 pathways; and induces EMT of NPC and acquisition of CSC-like properties
<i>LMP-2A</i>	Mimics constitutively active, antigen-independent BCR signaling through constitutive activation of the ERK/MAPK pathway <sup>224</sup> ; blocks antigen-dependent BCR signaling; induces B-cell lymphoma in transgenic condition; is important but not essential for <i>in vitro</i> primary B-lymphocyte growth transformation; rescues the LMP-1-generated impairment in germinal center in the response to antigen in animals; confers resting B cells sensitive to NF- $\kappa$ B inhibition and apoptosis; suppresses differentiation and promotes epithelial cell spreading and motility in epithelial cells; and enriches cancer stem cell-like population
<i>EBER</i>	Most abundant EBV-encoded noncoding RNAs; augments colony formation and induces growth; confers cells resistance to PKR-dependent apoptosis; induces cytokines and modulates innate immune response; binds to La, PKR, L22, PRR and RIG-I; and EBER-mediated RIG-I activation likely contributes to EBV oncogenesis. EBER blockades of PKR-mediated phosphorylation of eIF2 $\alpha$ results in blockage of eIF2 $\alpha$ -mediated inhibition of protein synthesis and resistance to IFN $\alpha$ -induced apoptosis
<i>miRNAs</i>	Transcribed from BART and BHRF1; validated targets include Bim, BRUCE, CXCL11, DICER1, PUMA; has a role in sustaining latently infected cells. BHRF1 miRNA and BART miRNAs interfere with apoptosis. The miR-BART15-3p promoted apoptosis 331

Abbreviations: BART, *Bam*HI-A region rightward transcript; BHRF1, *Bam*HI fragment H rightward open reading frame 1; CSC, cancer stem cell; DLBCL, diffuse large B-cell lymphoma; EBER, EBV-encoded nuclear antigen; EBV, Epstein-Barr virus; eIF2 $\alpha$ , eukaryotic initiation factor 2 $\alpha$ ; EMT, epithelial-mesenchymal transition; ERK, extracellular signal-regulated kinase; IFN, interferon; JNK, c-Jun N-terminal kinase; LMP, latent membrane protein; MAPK, mitogen-activated protein kinase; NF- $\kappa$ B, nuclear factor- $\kappa$ B; NPC, nasopharyngeal carcinoma; LP, leader protein; PKR, RNA-dependent protein kinase; PRR, pattern-recognition receptors; RBPJ, recombination signal-binding immunoglobulin  $\kappa$ J region; RIG-1, retinoic acid-inducible gene 1.

and LMP-2 expression likely contributes to cell survival by activation of nuclear factor- $\kappa$ B (NF- $\kappa$ B) and phosphatidylinositol 3 kinase (PI3K) pathways.<sup>59–75</sup> Moreover, EBERs are expressed in latency types III, II and I and are implicated in the survival of latency I BL cells.<sup>61,76–79</sup> Thus, EBV gene expression is likely critical for the growth and survival of EBV-associated malignancies (see Table 1).

## EBV-ENCODED NUCLEAR ANTIGEN-1

### EBNA-1 roles

EBNA-1 is expressed in all forms of latent EBV infection; it is essential for efficient EBV genome replication, persistence and transcription in dividing cells<sup>80–83</sup> and binds to and uses nucleolin and nucleophosmin (NPM) for EBNA-1-dependent transcriptional activation and genome persistence.<sup>84,85</sup> EBNA-1 is the only nuclear EBV antigen expressed in both latent and lytic modes of infection and contributes to the latent infection

in multiple ways. EBNA-1 suppresses spontaneous lytic reactivation in latent infection status;<sup>86</sup> however, it interacts with and disrupts promyelocytic leukemia (PML) nuclear bodies and also promotes lytic infection. EBNA-1 induces a family of microRNAs (let-7 microRNAs (miRNAs)), which in turn decreases the level of the cellular protein Dicer and inhibits the reactivation of latent EBV and may increase metastasis.<sup>87</sup> EBNA-1 in NPC and GC induces the loss of PML nuclear bodies, and decreased p53 activation and apoptosis in response to DNA damage.<sup>86,88</sup>

EBNA-1 binds to viral DNA elements and cellular promoters,<sup>89,90</sup> activates EBV viral Cp and Wp promoters, inhibits Qp promoters,<sup>91</sup> upregulates STAT1 (signal transducers and activators of transcription 1), whose expression correlates with major histocompatibility complex class I and II increase, downregulates tumor growth factor- $\beta$  signaling pathways, reduces SMAD2, a tumor growth factor- $\beta$  signaling

mediator protein tyrosine phosphatase receptor K,<sup>92,93</sup> upregulates CCL20 in HL,<sup>94</sup> inhibits the canonical NF- $\kappa$ B pathway by inhibiting IKK (IkB kinase) phosphorylation in NPC<sup>95</sup> and enhances activity of the AP-1 transcription factor (TF) in NPC cells by EBNA-1 binding to the promoters of c-Jun and ATF2<sup>96</sup> (see Table 1).

### Domains of EBNA-1

EBNA-1 encodes 641 amino acids (a.a.) from a prototype EBV strain.<sup>97</sup> EBNA-1 a.a. 2–30 have no known function and are dispensable for replication, DNA binding, transactivation and persistence.<sup>98</sup> Both arginine-glycine (RG)1 (a.a. 33–89) and RG2 (a.a. 328–386)<sup>99–106</sup> are necessary, sufficient and essential for efficient association of EBNA-1 with host chromosomes and EBNA-1-dependent transcription of latent genes, and for EBV oriP (an Origin of Plasmid replication) genome persistence. An almost inseparable dimerization domain (DD) and oriP DNA-binding domain (a.a. 459–607) bind specifically to EBV oriP, an enhancer of the transcription and origin of viral genome replication, and thereby brings to chromosomes. The dimerization domain/DNA-binding domain has central functions in DNA binding, transcription, persistence and replication.

RG1 and RG2 are separated by an irregular hydrophobic glycine-alanine repeats domain.<sup>107–109</sup> Deletion of the entire glycine-alanine repeats has no discernible effect on EBNA-1 abundance or functional interaction with oriP. The glycine-alanine domain minimizes translation,<sup>110</sup> binds to proteasomes and inhibits EBNA-1 proteolysis.<sup>111–113</sup> As a consequence of both decreased synthesis and very slow degradation, EBNA-1 peptides are poorly presented in the context of major histocompatibility complex class I. Cells expressing EBNA-1 are therefore partially protected from recognition by CD8 cytotoxic T lymphocytes.<sup>112–117</sup>

The EBNA-1 dimerization and DNA-binding domain (a.a. 459–607), were crystallized, bound to cognate DNA sites and resolved at 2.2 Å.<sup>104,106</sup> EBNA-1's essential role in EBV episome replication, transcription and persistence requires EBNA-1 homodimerization and DNA binding.<sup>106</sup> This domain mediates EBNA-1 interaction with oriP and supplementary sequence for replication (Rep\*), and also EBV Qp, the promoter for EBNA-1 transcription in latencies I and II.<sup>82,118–123</sup> EBNA-1 a.a. 379–386 is a nuclear localization sequence;<sup>99</sup> K379 and R380 are essential components and S385 phosphorylation has an upregulatory effect on nuclear import, whereas S383 and S386 phosphorylation inhibits nuclear import.<sup>124</sup> EBNA-1 a.a. 379–641 is also a dominant-negative inhibitor of EBNA-1 interaction with cognate DNA, resulting in decreased EBNA-1-dependent transcription and episome maintenance.<sup>125–130</sup> Dominant-negative EBNA-1 proteins and EBNA-1 antisense oligonucleotide or RNA interference inhibition of EBNA-1 result in EBV genome loss and abrogation of tumor cell growth and survival, indicating that EBNA-1 inhibition is a valid target for prevention or treatment of EBV-associated diseases.

### EBNA-1 binds to viral element and host chromosomes to tether for replication and maintenance of genome

EBV episomes persist in dividing malignant and non-malignant cells through EBNA-1 interaction with multiple cognate sites in EBV oriP DNA.<sup>81,82,122,131,132</sup> OriP comprises a family of repeats and a dyad symmetry. EBNA-1 interaction with oriP enables EBV DNA replication once per cell cycle.<sup>133–137</sup> The family of repeats and dyad symmetry are required for efficient episome persistence and transcriptional activation in infected cells.<sup>80–83,91,131,138–141</sup> The family of repeats is an EBNA-1-dependent enhancer,<sup>91,141–145</sup> whereas dyad symmetry is the site of initiation of EBV episome DNA replication (see Table 1).

### EBNA-1-interacting proteins

EBNA-1 RG1/2 interactions with hEBP2 (human EBNA-1-binding protein 2), P32/TAP (protein 32KD/HIV TAT-associating protein), Nap1, Karyopherin  $\alpha$ 2, PRMT5 and PRMT1 (protein methyl transferase-5 and -1), nucleolin and NPM<sup>146–152</sup> are implicated in transcriptional activation (hEBP2, p32/TAP, Karyopherin, PRMT5, PRMT1, nucleolin and NPM) or episome maintenance (hEBP2, Nap1, nucleolin and NPM). EBNA-1 a.a. 395–450 binds to host USP7 (ubiquitin-specific protease 7)<sup>148</sup> and forms a quaternary complex with USP7, GMPSC and EBV oriP DNA,<sup>153</sup> and this interaction alters histone modification at oriP, disrupts p53 and also the PML levels.<sup>154</sup> EBNA-1 a.a. 387–394 interacts with the host CK2 kinase  $\alpha$ ,  $\alpha'$  and  $\beta$ , and this interaction leads to the disruption of PML bodies. EBNA-1 also associates with PML proteins. The EBNA-1–CK2 complex phosphorylates PML proteins and triggers the polyubiquitylation and degradation of PML.<sup>155</sup> EBNA-1 also binds to NAP1, template-activating factor- $\beta$ /SET, CK2 and PRMT5.<sup>148</sup> EBNA-1 interacts with NPM, heterogeneous ribonucleoproteins and La protein.<sup>156</sup> EBNA-1 association with NPM contributes to the EBNA-1 transactivation function.<sup>84</sup>

### EBNA-LP AND EBNA-2

EBNA-2 and EBNA-LP are coexpressed soon after EBV infection in B cells,<sup>39</sup> are essential for B-cell transformation to LCL and LCL outgrowth<sup>41,42,157</sup> and cooperatively activate viral and cellular gene transcriptions for transformation.<sup>158,159</sup> Both LP and EBNA-2 associate with the transcriptional factor and the linking factors bound to upstream DNA elements of cMyc and also cMyc-regulated genes, forming a long-range DNA looping, which ultimately leads to cell cycle entry for proliferation.<sup>39,160,161</sup>

Recombination signal-binding immunoglobulin  $\kappa$ J region (RBPJ) protein associates with the NCoR repressor and is thus inherently a transcription repressor. Host DNA carries ~ 20 000 and ~ 10 000 sites, where LP or EBNA-2 and RBPJ bind (LP or EBNA-2 sites and RBPJ sites, respectively). A considerable fraction of LP sites were colocalized with EBNA-2 sites. LP and EBNA-2 sites are primarily located at or near the transcriptional start site, whereas EBNA-2 sites are more at the enhancer or intergenic region. LP sites were enriched for sites of B-cell



TFs including YY1, SP1, PAX5, BATF, IRF4, ETS1, RAD21, PU.1, CTCF, RBPJ, ZNF143, SMC3, NF- $\kappa$ B, TBLR and EBF. The CTCF as a transcription insulator associates with YY1, RAD21 and SMC3 to mediate long-range chromatin interactions (DNA linking) and promoter derepression.<sup>162</sup> In addition, LP sites were marked by RNAPII and histone acetylase P300, and also by activated histone tags such as H3K4me3, H3K27ac, H2Az and H3K9ac, indicative of LP sites being activated transcriptional sites. EBA2 induces cMyc transcription within 24 h after EBV infection of resting B cells (see Table 1).

### EBV-encoded nuclear antigen-LP

By costimulation of EBNA-2-dependent transcription, LP coactivates EBNA-2 transcriptional activation,<sup>163</sup> associates with EBNA-2, HA95 and Hsp70/72,<sup>164,165</sup> associates with and relocates 14-3-3 and histone deacetylase 4,<sup>166</sup> displaces Sp100 and Hp1 $\alpha$  from ND10 bodies and disrupts matrix-associated deacetylase bodies, dismisses repressor complex (NCoR/HA95) from promoter or enhancer sites and shuttles them from the nuclei to the cytoplasm.<sup>158,160,164,166</sup> This LP dismissal of NCoR and RBPJ repressors reduces the occupancy of repressors NCoR and RBPJ at EBNA-2 sites without altering EBNA-2 occupancy. However, LP and EBNA-2 do not affect each other's association with the enhancer or promoter.<sup>158</sup> These multiple complexes load on or near promoter sites and increase activated marks on the histone, leading to transcriptional activation for EBV-dependent efficient cell transformation<sup>166</sup> (see Table 1).

### EBV-encoded nuclear antigen-2

The EBNA-2 does not directly bind to DNA but instead associates with viral (LP) and cellular factors (RBPJ transcriptional repressor and ZNF143)<sup>167</sup> for transcriptional activation;<sup>168</sup> it associates with NCoR-deficient RBPJ and increases RBPJ binding to DNA, recruiting cellular TFs to EBNA-2 sites in the enhancer or promoter clustered with RBPJ EBF, ETS1, ZNF143, PU.1, NF- $\kappa$ B and RUNX1 sites.<sup>158,161</sup>

Similar to LP, EBNA-2 adds up the activation mark H3K4me1 on the histone, depletes the nucleosome, recruits transcriptional factors, coactivators and histone acetylases<sup>161,167,169,170</sup> and links the EBNA-2 site to target promoters by associating with RBPJ and other factors (see Table 1).

## LATENT MEMBRANE PROTEIN-1

### LMP-1 roles

LMP-1 and LMP-2A mimic CD40 and B-cell receptor (BCR) signaling, respectively, on B cells. EBV infection rescues BCR-negative, proapoptotic germinal center B cells from apoptosis.<sup>171</sup> LMP-1 is expressed in LCLs, HLs and undifferentiated NPCs but not GCs, and also during EBV replication; it is a major EBV-encoded oncogene and activates NF- $\kappa$ B, c-Jun N-terminal kinase (JNK) and p38 pathways;<sup>54,57,58,172</sup> it transforms primary rodent fibroblasts and is essential for EBV-mediated transformation; it induces an anchorage-independent growth with increased tumor formation after subcutaneous

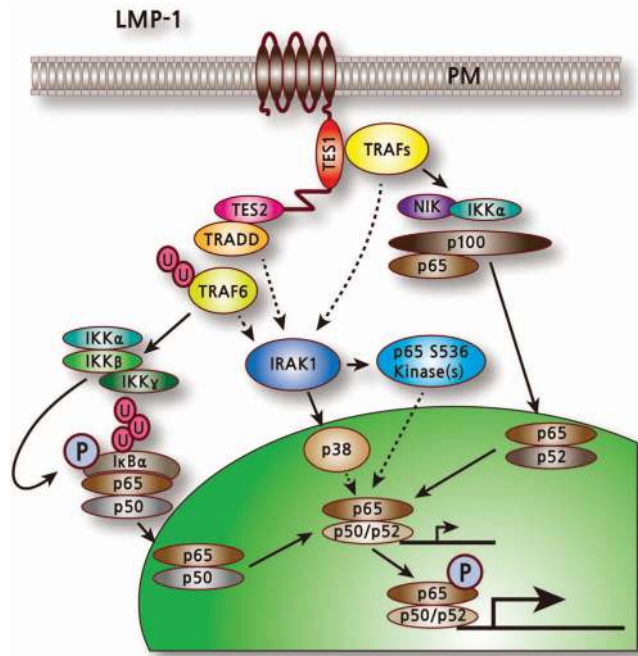
inoculation into nude mice, and also has effects on epithelial cell differentiation;<sup>60,173–188</sup> it upregulates surface molecules ICAM1, LFA1, CD40, CD21 and CD23 and downregulates CD10 expression, membrane ruffling and adhesion.<sup>189–200</sup>

LMP-1 is a major EBV-encoded oncogene and activates NF- $\kappa$ B, JNK and p38 pathways *in vitro* and *in vivo*; it increases the telomerase activity via cMyc induction<sup>201</sup> and promotes migration of NPC cells;<sup>202</sup> it induces epithelial–mesenchymal transition of NPC and acquisition of cancer stem cell-like properties<sup>202</sup> and inhibits LKB1-AMPK1 tumor suppressor pathways in NPC through the phosphorylation of LKB1 at serine 428, with subsequent suppression of the phosphorylation of AMPK.<sup>203</sup> LMP-1 induces a proapoptotic Bmi-1 (Bcl-2-interacting mediator of cell death) in HL cells, which is downregulated by EBNA-3A and EBNA-3C.<sup>204,205</sup> LMP-1 induces IL8 expression through the NF- $\kappa$ B binding site, which may contribute in part to angiogenesis in NPC.<sup>206</sup> LMP-1 induces a proapoptotic Bmi-1 in HL cells, which is downregulated by EBNA-3A and EBNA-3C.<sup>204,205</sup> LMP-1 induces IL-8 expression through the NF- $\kappa$ B binding site, which may contribute in part to angiogenesis in NPC.<sup>206</sup> In LMP-1-nonexpressing GC, BAF1 likely has a growth promoter activity via activation of NF- $\kappa$ B in GC<sup>207</sup> (see Table 1).

### LMP1 structure, domain and interactions

The key LMP-1 functional domains are: (i) six transmembrane domains (TM1–6), which mediate raft association, constitutive aggregation and constitutive signaling; and (ii) two transformation effector sites (TES1 and TES2). LMP-1 oligomerizes on the plasma membrane through TM1 interaction with TM3–6, forming a ligand-independent signaling complex. TM1–4 is important for wild-type LMP-1 C-terminus-mediated NF- $\kappa$ B activation, whereas TM3–4, TM5–6 or TM3–6 is dispensable.<sup>208</sup> LMP-1 (also LMP-2) is palmitoylated at cysteine residues, but palmitoylation is not required for raft association or signaling (Figure 1).<sup>209</sup>

LMP-1 C-terminus domains have two transformation effector sites (TES 1 and TES2), which mediate tumor necrosis factor receptor signaling. TES1 and TES2 are required for efficient NF- $\kappa$ B- and EBV-mediated B-cell transformation. The PQQAT motif in TES1 associates with TRAF1, 2, 3 and 5, to which CD40 binds and thus provides mechanisms for LMP-1 to act as a constitutively active CD40 decoy for TRAFs. The TES1 interaction with these TRAFs induces an NF- $\kappa$ B noncanonical pathway by phosphorylating NIK, IKK $\alpha$  and p100, which in turn process p100 to p52. TES1 is required for long-term outgrowth, whereas TES2 associates with TRADD and functionally links to TRAF6. TES2 is essential for the initial phase of transformation and activates the classical NF- $\kappa$ B pathway. The direct or indirect association of TRADD with TRAF6 activates TRAF6 E3 ligase, TAK1 and TAK1-like kinase. The TAK1 kinases activate IKK $\beta$ , which phosphorylates I $\kappa$ B $\alpha$ , leading to I $\kappa$ B $\alpha$  ubiquitylation and degradation, and release of p50/p65 complexes to the nucleus. Both TES1 and TES2, possibly through TRAF3 and TRAF6, respectively, also induce IRAK1-mediated activation of p38 and other kinase(s) that



**Figure 1** Latent membrane protein-1 (LMP1)-mediated activation of natural factor- $\kappa$ B (NF- $\kappa$ B) signaling.

phosphorylate p65. IRAK1 is required for both p38 activation and p65/RelA phosphorylation. LMP-1 activation of NF- $\kappa$ B is largely IRAK1 and TRAF6 dependent, whereas tumor necrosis factor receptor activation of NF- $\kappa$ B is largely IRAK1 and TRAF6 independent (Figure 1).<sup>70,172,210–219</sup>

## LATENT MEMBRANE PROTEIN-2A

### LMP-2A roles in B cells

LMP-2A mimics constitutively active, antigen-independent, BCR signaling. It can also block an antigen-dependent BCR signaling that can be experimentally initiated by surface immunoglobulin crosslinking to increase calcium mobilization and by lytic reactivation of EBV;<sup>62,220,221</sup> it binds BCR-associated kinases and Nedd4 family ubiquitin-protein ligases, which downmodulate LMP-2A activity by ubiquitinating LMP-2A,<sup>222</sup> prevents BCR recruitment to lipid rafts, thereby abrogating BCR function, does not require palmitoylation to localize to buoyant complexes or for function,<sup>223</sup> requires a cholesterol for LMP-2A trafficking and stability, provides a pre-BCR-like signal to developing B cells through constitutive activation of the extracellular signal-regulated kinase/mitogen-activated protein kinase pathway,<sup>224</sup> and requires LMP-2A immunoreceptor tyrosine-based activation motif and PY motifs for an Ag-dependent BCR block and subsequent activation of the PI3K/AKT; in addition,  $\beta$ -catenin accumulation prevents the switch from latent to lytic reactivation.<sup>225</sup>

LMP-2A promotes B-cell growth,<sup>62</sup> induces B lymphoma, has a transformation ability *in vitro* and *in vivo*, which was blocked by an immunoreceptor tyrosine-based activation motif LMP-2A mutant, the Syk inhibitor or Syk-specific small interfering RNA,<sup>226</sup> and is important but not essential for

*in vitro* primary B-lymphocyte growth transformation, latent infection and lytic virus replication *in vitro*<sup>43,227,228</sup> but is essential for growth transformation of germinal center B cells, which do not express the genuine BCR because of deleterious somatic hypermutations in their immunoglobulin genes;<sup>221</sup> it increases the prosurvival and anti-inflammatory cytokine IL-10 via PI3K,<sup>229</sup> upregulates genes associated with cell cycle induction and inhibition of apoptosis and downregulates genes associated with B-cell-specific factors and immunity similarly to those in HRS cells of HL,<sup>230</sup> and it counteracts the antiproliferative effect of the S10A mutant to promote the S-phase entry.<sup>231</sup>

LMP-2A rescues the LMP-1-generated impairment in germinal center in response to antigen in LMP-1/2A animals,<sup>232</sup> makes resting B cells sensitive to NF- $\kappa$ B inhibition and apoptosis,<sup>233</sup> potentiates cMyc to promote cell cycle progression and hyperproliferation by downregulating cyclin-dependent kinase inhibitor p27 (kip1) in a proteasome-dependent manner,<sup>231</sup> bypasses p53 inactivation in a cMyc-induced lymphomagenesis model,<sup>234,235</sup> is down-regulated by c-CBL ubiquitin ligase (E3), a critical negative regulator in the BCR signal pathway,<sup>236</sup> cooperates with Notch 1 to alter B-cell identity *in vivo*,<sup>237</sup> activates its own promoter and Notch promoter in an EBNA-2-independent manner,<sup>224</sup> enhances the development of autoimmune diseases in transgenic LMP-2A expression in B cells,<sup>238</sup> induces hypersensitivity to TLR stimulation, leading to the activation of autoantigen-reactive B cells through the BCR/TLR pathway,<sup>34</sup> bypasses anergy induction in response to low levels of soluble antigen, induces NF- $\kappa$ B nuclear translocation independent of BCR crosslinking<sup>239</sup> and transactivates the human endogenous retrovirus HERV-K18 superantigen<sup>240</sup> (see Table 1).

### LMP-2A in epithelial cells

LMP-2A suppresses differentiation,<sup>74</sup> promotes epithelial cell spreading and motility together with LMP-2B,<sup>241</sup> leads to the transcriptional repression of the *hTERT* gene,<sup>242</sup> contributes to anoikis resistance,<sup>243</sup> enriches cancer stem cell-like population from fibroblasts,<sup>244</sup> enhances epithelial–mesenchymal transition in NPC via induction of metastatic tumor antigen (MTA1) and mammalian target of rapamycin signaling,<sup>245</sup> induces the detected form of P63a (deltaP63) that impairs epithelial cell differentiation,<sup>246</sup> activates DNA methyltransferase 1 leading to promoter hypermethylation of the *PTEN* gene in GC,<sup>247</sup> is frequently detected in NPC and induces UDP-glucose dehydrogenase expression via ERK and PI3K/AKT pathways but not JNK and p38 pathways,<sup>248</sup> does not induce anchorage-independent cell growth in a human keratinocyte cell line but does in a human GC cell line via the constitutive Ras/PI3K/AKT pathway<sup>67</sup> and limits the interferon together with LMP-2B by targeting interferon receptors for degradation<sup>249</sup> (see Table 1).

### Structure, domain and interaction

EBV encodes two nearly identical LMP-2 with the same TMs (LMP-2A and LMP-2B).<sup>250</sup> The LMP-2A isoform has 12 TMs

and extra 119 a.a. at the amino-terminal cytoplasmic signaling domain, whereas the LMP-2b isoform is identical but lacks the cytoplasmic signaling domain.<sup>250</sup> LMP-2A/B are constitutively expressed primarily in the plasma membrane, and also in cytoplasmic location, in all EBV-infected cells.<sup>250,251</sup> LMP-2 associates with and is a substrate for a B-lymphocyte tyrosine kinase Lyn and Syk protein tyrosine kinases<sup>252</sup> through the first 167 of the LMP-2A 497 a.a., colocalizes with the cellular tyrosine-phosphorylated proteins on the plasma membrane and is also serine and threonine phosphorylated.<sup>62,253</sup> Although in B cells LMP-2 is tyrosine phosphorylated by the Src family kinase (Lyn, Syk), in epithelial cells it is mediated by the C-terminal Src kinase, which is triggered by epithelial cell adhesion to extracellular matrix proteins.<sup>254</sup> The immunoreceptor tyrosine-based activation motif contributes to LMP-2A phosphorylation and participates in signal transduction events in epithelial cells. The BCR block by LMP-2A is bypassed by raising intracellular-free  $Ca^{2+}$  levels with an ionophore or by activating protein kinase C with phorbol 12-myristate 13-acetate. LMP-2A, but not LMP-2B, mediates this effect on calcium mobilization.<sup>225</sup> LMP-2A is secreted through exosomes similarly to LMP-1.<sup>222</sup> Cholesterol depletion from the plasma membrane increases LMP-2A abundance and LMP-2A exosome secretion and also blocks endocytosis, phosphorylation and ubiquitylation of LMP-2A, indicating that cholesterol-dependent LMP-2A trafficking determines the fate of LMP-2A.<sup>222</sup>

### Latent membrane protein-2B

LMP-2B interferes with LMP-2A functions, increases lytic activation from its latent forms upon BCR crosslinking, lowers the threshold of BCR crosslinking required to induce lytic EBV infection, colocalizes with LMP-2A and restores LMP-2A-mediated  $Ca^{2+}$  mobilization upon BCR crosslinking. Collectively, LMP-2B negatively regulates LMP-2A, the function in preventing the switch from latent to lytic EBV replication.<sup>255,256</sup>

### EBNA-3 FAMILY

EBNA-3A, EBNA-3B and EBNA-3C gene families have the same promoter, similar gene structures, are similarly regulated and regulate host transcription. Each has a domain for binding to RBPJ, a cellular sequence-specific DNA-binding TF that mediates EBNA-2 or Notch binding to DNA.<sup>257</sup> All EBNA-3 families are coactivators of EBNA-2. EBNA-3C functions as a coactivator and corepressor. The coactivation activities EBNA-3A and EBNA-3B are around half that of EBNA-3C.<sup>258</sup> Although EBNA-3B is dispensable for B-cell transformation, both EBNA-3A and EBNA-3C are essential.<sup>49,50,259</sup> Despite the similarity, EBNA-3C deletion can only be rescued by 3C but not by EBNA-3A or EBNA-3B expression in the restoration of LCL growth, and EBNA-3A deletion can only be rescued by EBNA-3A.<sup>49,50,260,261</sup>

In contrast to EBNA-2, which tethers to DNA via the RBPJ bridge, EBNA-3A and EBNA-3C associations with RBPJ inhibits RBPJ recruitments to DNA, downregulates cMyc transcription and blocks EBNA-2 activation effects.<sup>46,262,263</sup>

EBNA-3C residues a.a. 130–159 bind to IRF4 or IRF8,<sup>264</sup> and coactivate the EBV LMP-1 promoter with EBNA-2 through an SPI1 site in the absence of RBPJ<sup>258,265</sup> (see Table 1).

### EBV-encoded nuclear antigen-3A

Both EBNA-3A and EBNA-3C repress the EBNA-2-activated transcription by direct interaction with RBPJ proteins, a cellular DNA-binding factor known to recruit EBNA-2 to EBNA-2-responsive genes. EBNA-3A represses contiguous clusters arrayed in the human genome by polycomb group-mediated epigenetic silencing.<sup>266</sup> The *CXCL10* and *CXCL9* chemokines and their receptors (CXCR3/4) can control herpesvirus infections. EBNA-3A associates with intergenic enhancers located between *CXCL10* and *CXCL9* and displaces the transactivator EBNA-2, leading to a rapid transcriptional shutdown, which is also because of a delayed gain of polycomb group histone marks.<sup>266</sup>

A Bim is a cellular inducer of apoptosis. In the absence of Bim, EBNA-3A and EBNA-3C provide no survival advantage.<sup>205</sup> The level of Bim is a critical regulator of B-cell survival and reduced expression is a major determinant of LPD in mice and humans. cMyc can induce apoptosis via Bim. EBNA-3A and EBNA-3C likely repress Bim expression without altering Bim protein or RNA stability, but through reduced histone acetylation and increased DNA methylation on the *Bim* promoter, which was preceded by polycomb protein-mediated repression.<sup>267</sup>

EBNA-3A binds to the cMyc-interacting DNA-binding zinc-finger protein-1. EBNA-3A interaction with cMyc-interacting DNA-binding zinc-finger protein-1 prevents cMyc-interacting DNA-binding zinc-finger protein-1 from binding to a coactivator, NPM, resulting in a decrease in *CDKN2B* transcription.<sup>268</sup> EBNA-3A or EBNA-3C inactivation in LCLs induces G<sub>1</sub> arrests resulting from EBNA-3A/C-mediated induction of *CDKN2A p16<sup>INK4A</sup>* expression.<sup>260,261,269–272</sup> Because EBNA-2 activates cMyc expression through RBPJ, and associates less stably with RBPJ compared with EBNA-3A, EBNA-3B or EBNA-3C, some EBNA-3 effects on transcription and LCL growth may be in limitation of EBNA-2 access to RBPJ (10–14, 18–21). EBNA-3A or EBNA-3C association with RBPJ, but not with the adenovirus E1a C-terminal binding protein, is essential for LCL growth.<sup>260,261,269,270,273</sup> Similar to EBNA-3C, EBNA-3A interacts with many cellular partners, including PU.1, Spi-B, histone deacetylase 1, DP103, prothymosin- $\alpha$ , p300, Nm23-H1 and SUMO1, as well as SUMO3, cyclin A, SCF-Skp2 ubiquitin ligase, pRb, Chk2, Mdm2 and MRS18-2. Some of these interactions repress *CDKN2A p16<sup>INK4A</sup>* or *p14<sup>ARF</sup>* for enabling LCL growth.<sup>270</sup> EBNA-3A and EBNA-3C cooperatively repress a transcription of the *p16<sup>INK4A</sup>* and *p14<sup>ARF</sup>* tumor suppressors, allowing cell cycle entry<sup>270</sup> (see Table 1).

### EBV-encoded nuclear antigen-3B

Among six latency-associated EBNAs, only EBNA-3B is completely dispensable for B-cell transformation *in vitro* and could be a tumor suppressor. In contrast to EBNA-3A and EBNA-3C,



both of which repress transcriptions of tumor suppressors  $p14^{ARF}$ ,  $p16^{INK4A}$  and chemokine CXCL10, EBNA-3B upregulates CXCL10 and has a growth inhibitory role. EBNA-3B knockout induces diffuse large B-cell lymphoma-like tumors in humanized NOD/SCID/ $\gamma c^{-/-}$  mice reconstituted with the human immune system with the expansion of EBV-specific T cells. The B cells infected with EBNA-3B knockout EBV expand more rapidly and secrete less T-cell chemoattractant CXCL10, leading to inefficient recruitment of T cells *in vitro* and T-cell-mediated killing *in vivo*. Natural human B lymphoma cell lines from patients with truncated EBNA-3B EBV exhibited similar genotypic and phenotypic characteristics, including reduced CXCL10 secretion. Importantly, EBNA-3B-mutated B-cell lymphomas were frequently found. EBNA-3B is the EBV-encoded tumor suppressor whose inactivation drives lymphomagenesis and immune evasion<sup>274</sup> (see Table 1).

### EBV-encoded nuclear antigen-3C

EBNA-3C through N-terminal a.a. 50–400 is essential for LCL growth;<sup>50,273</sup> it coactivates the EBV LMP-1 promoter with EBNA-2 and host CXCR4 and CXCL12 gene expression but represses the EBV C promoter.<sup>265,275,276</sup>

EBNA-3C associates with SUMO-1, P300, prothymolysin (ProTalpha), histone deacetylase 1/2, metastatic suppressor NM23-H1 through EBNA-3C glutamine- and proline-rich domain, corepressor mSinA and NCoR, SCF-Skp2, cyclin A/D1<sup>277</sup> and cMyc, Gemin3 (also called DDX20 or DP103), p53, p53 regulatory proteins, the inhibitor of growth family proteins ING4/5, IRF4/8, aurora kinase B, H2AX and Pim-1;<sup>258,264,278–282</sup> it regulates chromatin remodeling via recruitment of histone (de)acetyltransferases, facilitates cell cycle entry, stabilizes Geminin3 and cMyc, induces the Mdm2-mediated p53 degradation and represses p53-dependent transactivation on its downstream genes  $p21$  and  $Bax$ , as well as p53- and E2F-mediated apoptosis in part through targeted regulation of interferon regulatory factors 4 and 8.

EBNA-3C also mediates the degradation of the retinoblastoma protein through an SCF cellular ubiquitin ligase, upregulates aurora kinase B transcription, increases aurora kinase B protein stability by reducing ubiquitylation of aurora kinase B and attenuates H2AX expression, stabilizes Pim-1 and Pim-1-mediated proteasomal degradation of the cell cycle inhibitor p21/WAF1, promoting cell proliferation, upregulates TCL1A and ITGA4, downregulates JAG1 and NCALD and cooperates with EBNA-3A in repressing Bim, a proapoptotic Bcl-2 family protein.<sup>264,267,273,283–287</sup>

EBNA-3C coactivation of EBNA-2 requires PU.1 site, but not RBPJ binding sites, in the LMP-1 promoter. The expression of chemokine CXCL12 and its receptor contributes to EBV-positive peripheral blood mononuclear cell growth in mice with severe combined immunodeficiency disease.<sup>288</sup> EBNA-3A- and EBNA-3C-mediated B-cell transformation is primarily through transcriptional deregulation of host genes. EBNA-3C and EBNA-3A repress  $p14^{ARF}$  and  $p16^{INK4A}$  transcription, which help in LCL growth. Depletion of  $p14^{ARF}$  and  $p16^{INK4A}$  or knockout of  $p16^{INK4A}$  supports LCL growth in the absence

of EBNA-3C.<sup>270,272</sup> Repressive activities of EBNA-3A and EBNA-3C are associated with histone modifications: EBNA-3A induces repressive histone mark H3K27me3, which is installed by polycomb group proteins at the  $CXCL10$  and  $CXCL9$  chemokine genes,<sup>266</sup> whereas EBNA-3C-mediated histone modifications are important for  $p14^{ARF}$  and  $p16^{INK4A}$  repression.<sup>289</sup>

Similar to EBNA-2 and LP, EBNA-3C regulates the viral and cellular gene transcription through interactions with cellular proteins including RBPJ<sup>264,265,290</sup> at 13 000 promoter and enhancer sites (called 3C sites). The 13 000 3C sites are located on EBV LMP-1, BIM and ITGA4 promoters and were highly colocalized with AICE (IRF4/BATF complex), EICE (IRF4/SPI1) and RUNX3. EBNA-3C interactions with AICE and EICE sites drive LCL proliferation.<sup>291</sup> EBNA-3C recruits Sin3A repressive complexes (Sin3A, histone deacetylases 1 and 2 and RBPJ) to the  $p14^{ARF}$  promoter to mediate  $p14^{ARF}$ , and  $p16^{INK4A}$  repression in cooperation with EBNA-3A.<sup>272</sup> EBNA-3C overcomes p16(INK4a) increase-driven proliferation block after EBV infection. In p16(INK4a)-null cells, functional EBNA-3C is dispensable for the outgrowth of LCLs.<sup>272</sup> EBNA-3C functions as a gene regulator in combination with TFs, mostly AICEs, EICEs and RUNX3.<sup>290–292</sup> EBV uses B-cell TFs to drive cell cycle entry for persistence or virus replication (see Table 1).

### EBV-ENCODED RNA

EBV genomes abundantly express noncoding EBV-encoded RNAs (called EBER1 and EBER2). EBERs are transcribed by host RNA polymerase III as small non coding nonpolyadenylated RNAs.<sup>293–296</sup> The role of EBERs in EBV-induced B-lymphocyte transformation has been contradictory. Earlier reports described nonessential roles of EBER for B-lymphocyte transformation.<sup>48,297</sup> However, a critical role was also demonstrated.<sup>298</sup> EBER expression augments colony formation and induces growth in *in vitro* or *in vivo* tumorigenesis,<sup>79,299–301</sup> resistance to RNA-dependent protein kinase (PKR)-dependent apoptosis<sup>302</sup> and cytokines including IL-10, IL-9, IGF1 and IL-6,<sup>303–306</sup> and modulates innate immune response.<sup>307,308</sup>

EBERs binds to La,<sup>293</sup> PKR, ribosomal protein L22 (also called as EAP),<sup>309</sup> pattern-recognition receptors, retinoic acid-inducible gene I (RIG-I), melanoma differentiation-associated gene-5<sup>307</sup> and AU-rich element binding factor 1.<sup>310</sup> EBER-mediated RIG-I activation likely contributes to EBV oncogenesis.<sup>307</sup>

EBERs in complex with La release from cells<sup>308</sup> and bind to the dephosphorylated PKR, which is double-stranded RNA-dependent and an interferon (IFN)-inducible serine/threonine kinase.<sup>311,312</sup> Antibody to La is implicated in SLE.<sup>293</sup> Viral infection-induced IFNs activate PKR, which phosphorylates the  $\alpha$ -subunit of the protein synthesis initiation factor eukaryotic initiation factor 2, leading to translational inhibition. EBER blockades of PKR-mediated phosphorylation of eukaryotic initiation factor 2 $\alpha$  result in the blockage of eukaryotic initiation factor 2 $\alpha$ -mediated inhibition of protein synthesis and resistance to IFN $\alpha$ -induced apoptosis.<sup>78,313,314</sup> Most EBERs



establish stable complexes with L22 *in vivo*, thereby modulating protein translation.<sup>315</sup> L22 and PKR compete for EBER binding and L22 interferes with EBER inhibition of PKR and EBER-induced gene expression.<sup>316</sup> Interaction of EBERs with RIG-I, AU-rich element binding factor 1 and pattern-recognition receptors could activate host innate immune responses.<sup>317</sup> EBER double-stranded RNA structures also activate RIG-mediated NF- $\kappa$ B and IRF-3 signaling and subsequently type I IFN induction. EBV latent infection is maintained by counterbalancing to IFN-mediated viral clearance through PKR inhibition. EBER induction of anti-inflammatory and growth-promoting cytokine IL-10 promotes cell growth and this process is a RIG-I-mediated IRF3-dependent but largely NF- $\kappa$ B-independent process (see Table 1).

### EBV-ENCODED MIRNAS

EBV genomes express many miRNAs from two regions of EBV's genome: BART and BHRF1 (*Bam*HI fragment H rightward open reading frame 1). The EBV genome transcribes at least 25 pre-miRNAs that encode 40 short single-stranded RNAs.<sup>318</sup> These miRNAs were expressed in a variety of EBV-infected malignant cells with abundance of individual miRNA being largely cell type specific. The BART transcript encodes miRNA. Although BART miRNA expression occurs in almost all types of EBV-associated latency cells, BHRF1-encoded miRNAs are quite restricted.<sup>319–322</sup>

Many of the EBV miRNA targets were validated. Cellular targets of EBV miRNAs include Bim (BCL2L11), which is targeted by BART-9, -11 and -12, BRUCE by BART15-3p, CASP3 by BART1-3p, CLEC2D by BART1-3p, CAPRN2 by BART13-3p, CXCL11 by BHRF1-3, DICER1 by BART6-5p, DAZAP2, DICE1, IPO7, PDE7A and PELI1 by BART-3, LY75 and SP100 by BART1-5p, PDCD1LG2 by BHRF1-2-5p, BART1-5p and 15-3p, PUMA by BART-5, T-bet(TBX21) by BART-20-5p, TOMM22 by BART-16, NLRP3 by BART-15 and ZNF451 by BHRF1-1.<sup>322</sup> CXCL-11, miR-BHRF1-3 target, is a chemokine that is induced by IFN-responsive reactive T cells and binds CXCR3, a common chemokine receptor for many chemokines expressed on T cells.<sup>323</sup> The miR-BART2-5p targets a stress-induced natural killer cell ligand, MICB, allowing EBV-infected cells to escape recognition and subsequent elimination.<sup>324,325</sup>

Most EBV miRNAs have the ability to sustain latently infected cells. BHRF1 miRNA facilitates progressive growth, *in vitro* transformation of infected cells and acute systemic EBV infection but not the overall oncogenic potential of EBV *in vivo*.<sup>326–328</sup> In addition, BHRF1 and BART miRNAs prevent primary B cells or BLs, respectively, from apoptosis.<sup>327,329</sup> In contrast, miR-BART15-3p promoted apoptosis.<sup>330</sup> Given that most of the EBV infections persist for a lifetime with asymptomatic penetration, viral miRNAs should also participate, at least in part, in the evasion from host immune surveillance (see Table 1).

### APPENDIX

EBV-induced immediate hyperproliferation of host cell mimics and induces strong ATM/Chk2-mediated DNA damage response, resulting in acute attenuation of infected B-cell growth, which should be bypassed or suppressed for efficient and ultimate immortalization by an EBV antigen. Biochemical and genetic study demonstrated that EBNA3C may function in overcoming the growth arrest.<sup>331</sup> Despite its high stability as a dimer in high salt condition, it has been recently shown that EBNA-1 DNA-binding and transactivation activity could be targeted by small molecules or peptides identified by high-throughput cell-based or *in silico* screens.<sup>332–336</sup>

### CONFLICT OF INTEREST

The authors declare no conflict of interest.

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