

REVIEW

Epstein–Barr virus latent genes

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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 1964.¹ The Epstein–Barr virus (EBV) infection is ubiquitous in adult humans.^{2–4} Higher titer of EBV antibody was evident in BL, lymphoproliferative diseases (LPDs), Hodgkin's lymphoma (HL), endemic nasopharyngeal carcinoma (NPC) and infectious mononucleosis.^{5–13} 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.^{14–33} 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).^{5–13,34,35} 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.^{27–33} 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.^{36–38}

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.^{39–58} 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- κ B, JNK and p38 pathways; is critical for EBV-mediated B-cell transformation, a major EBV-encoded oncogene; activates NF- κ 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 ²²⁴ ; 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- κ 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 α results in blockage of eIF2 α -mediated inhibition of protein synthesis and resistance to IFN α -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 α , eukaryotic initiation factor 2 α ; 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- κ B, nuclear factor- κ B; NPC, nasopharyngeal carcinoma; LP, leader protein; PKR, RNA-dependent protein kinase; PRR, pattern-recognition receptors; RBPJ, recombination signal-binding immunoglobulin κ J region; RIG-1, retinoic acid-inducible gene 1.

and LMP-2 expression likely contributes to cell survival by activation of nuclear factor- κ B (NF- κ B) and phosphatidylinositol 3 kinase (PI3K) pathways.^{59–75} Moreover, EBERs are expressed in latency types III, II and I and are implicated in the survival of latency I BL cells.^{61,76–79} 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^{80–83} and binds to and uses nucleolin and nucleophosmin (NPM) for EBNA-1-dependent transcriptional activation and genome persistence.^{84,85} 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;⁸⁶ 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.⁸⁷ EBNA-1 in NPC and GC induces the loss of PML nuclear bodies, and decreased p53 activation and apoptosis in response to DNA damage.^{86,88}

EBNA-1 binds to viral DNA elements and cellular promoters,^{89,90} activates EBV viral Cp and Wp promoters, inhibits Qp promoters,⁹¹ 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- β signaling pathways, reduces SMAD2, a tumor growth factor- β signaling

mediator protein tyrosine phosphatase receptor K,^{92,93} upregulates CCL20 in HL,⁹⁴ inhibits the canonical NF- κ B pathway by inhibiting IKK (IkB kinase) phosphorylation in NPC⁹⁵ and enhances activity of the AP-1 transcription factor (TF) in NPC cells by EBNA-1 binding to the promoters of c-Jun and ATF2⁹⁶ (see Table 1).

Domains of EBNA-1

EBNA-1 encodes 641 amino acids (a.a.) from a prototype EBV strain.⁹⁷ EBNA-1 a.a. 2–30 have no known function and are dispensable for replication, DNA binding, transactivation and persistence.⁹⁸ Both arginine-glycine (RG)1 (a.a. 33–89) and RG2 (a.a. 328–386)^{99–106} 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.^{107–109} 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,¹¹⁰ binds to proteasomes and inhibits EBNA-1 proteolysis.^{111–113} 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.^{112–117}

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.^{104,106} EBNA-1's essential role in EBV episome replication, transcription and persistence requires EBNA-1 homodimerization and DNA binding.¹⁰⁶ 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.^{82,118–123} EBNA-1 a.a. 379–386 is a nuclear localization sequence;⁹⁹ K379 and R380 are essential components and S385 phosphorylation has an upregulatory effect on nuclear import, whereas S383 and S386 phosphorylation inhibits nuclear import.¹²⁴ 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.^{125–130} 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.^{81,82,122,131,132} OriP comprises a family of repeats and a dyad symmetry. EBNA-1 interaction with oriP enables EBV DNA replication once per cell cycle.^{133–137} The family of repeats and dyad symmetry are required for efficient episome persistence and transcriptional activation in infected cells.^{80–83,91,131,138–141} The family of repeats is an EBNA-1-dependent enhancer,^{91,141–145} 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 α 2, PRMT5 and PRMT1 (protein methyl transferase-5 and -1), nucleolin and NPM^{146–152} 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)¹⁴⁸ and forms a quaternary complex with USP7, GMPSC and EBV oriP DNA,¹⁵³ and this interaction alters histone modification at oriP, disrupts p53 and also the PML levels.¹⁵⁴ EBNA-1 a.a. 387–394 interacts with the host CK2 kinase α , α' and β , 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.¹⁵⁵ EBNA-1 also binds to NAP1, template-activating factor- β /SET, CK2 and PRMT5.¹⁴⁸ EBNA-1 interacts with NPM, heterogeneous ribonucleoproteins and La protein.¹⁵⁶ EBNA-1 association with NPM contributes to the EBNA-1 transactivation function.⁸⁴

EBNA-LP AND EBNA-2

EBNA-2 and EBNA-LP are coexpressed soon after EBV infection in B cells,³⁹ are essential for B-cell transformation to LCL and LCL outgrowth^{41,42,157} and cooperatively activate viral and cellular gene transcriptions for transformation.^{158,159} 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.^{39,160,161}

Recombination signal-binding immunoglobulin κ 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- κ 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.¹⁶² 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,¹⁶³ associates with EBNA-2, HA95 and Hsp70/72,^{164,165} associates with and relocates 14-3-3 and histone deacetylase 4,¹⁶⁶ displaces Sp100 and Hp1 α 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.^{158,160,164,166} 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.¹⁵⁸ 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 transformation¹⁶⁶ (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)¹⁶⁷ for transcriptional activation;¹⁶⁸ 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- κ B and RUNX1 sites.^{158,161}

Similar to LP, EBNA-2 adds up the activation mark H3K4me1 on the histone, depletes the nucleosome, recruits transcriptional factors, coactivators and histone acetylases^{161,167,169,170} 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.¹⁷¹ 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- κ B, c-Jun N-terminal kinase (JNK) and p38 pathways;^{54,57,58,172} 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;^{60,173–188} it upregulates surface molecules ICAM1, LFA1, CD40, CD21 and CD23 and downregulates CD10 expression, membrane ruffling and adhesion.^{189–200}

LMP-1 is a major EBV-encoded oncogene and activates NF- κ B, JNK and p38 pathways *in vitro* and *in vivo*; it increases the telomerase activity via cMyc induction²⁰¹ and promotes migration of NPC cells;²⁰² it induces epithelial–mesenchymal transition of NPC and acquisition of cancer stem cell-like properties²⁰² 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.²⁰³ 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.^{204,205} LMP-1 induces IL8 expression through the NF- κ B binding site, which may contribute in part to angiogenesis in NPC.²⁰⁶ LMP-1 induces a proapoptotic Bmi-1 in HL cells, which is downregulated by EBNA-3A and EBNA-3C.^{204,205} LMP-1 induces IL-8 expression through the NF- κ B binding site, which may contribute in part to angiogenesis in NPC.²⁰⁶ In LMP-1-nonexpressing GC, BAF1 likely has a growth promoter activity via activation of NF- κ B in GC²⁰⁷ (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- κ B activation, whereas TM3–4, TM5–6 or TM3–6 is dispensable.²⁰⁸ LMP-1 (also LMP-2) is palmitoylated at cysteine residues, but palmitoylation is not required for raft association or signaling (Figure 1).²⁰⁹

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- κ 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- κ B noncanonical pathway by phosphorylating NIK, IKK α 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- κ 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 β , which phosphorylates I κ B α , leading to I κ B α 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

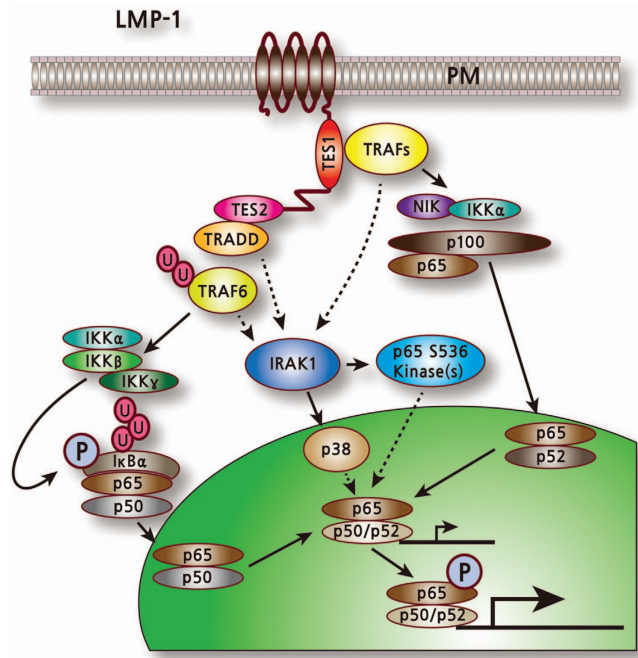


Figure 1 Latent membrane protein-1 (LMP1)-mediated activation of natural factor- κ B (NF- κ B) signaling.

phosphorylate p65. IRAK1 is required for both p38 activation and p65/RelA phosphorylation. LMP-1 activation of NF- κ B is largely IRAK1 and TRAF6 dependent, whereas tumor necrosis factor receptor activation of NF- κ B is largely IRAK1 and TRAF6 independent (Figure 1).^{70,172,210–219}

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;^{62,220,221} it binds BCR-associated kinases and Nedd4 family ubiquitin-protein ligases, which downmodulate LMP-2A activity by ubiquitinating LMP-2A,²²² prevents BCR recruitment to lipid rafts, thereby abrogating BCR function, does not require palmitoylation to localize to buoyant complexes or for function,²²³ 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,²²⁴ 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, β -catenin accumulation prevents the switch from latent to lytic reactivation.²²⁵

LMP-2A promotes B-cell growth,⁶² 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,²²⁶ and is important but not essential for

in vitro primary B-lymphocyte growth transformation, latent infection and lytic virus replication *in vitro*^{43,227,228} 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;²²¹ it increases the prosurvival and anti-inflammatory cytokine IL-10 via PI3K,²²⁹ 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,²³⁰ and it counteracts the antiproliferative effect of the S10A mutant to promote the S-phase entry.²³¹

LMP-2A rescues the LMP-1-generated impairment in germinal center in response to antigen in LMP-1/2A animals,²³² makes resting B cells sensitive to NF- κ B inhibition and apoptosis,²³³ potentiates cMyc to promote cell cycle progression and hyperproliferation by downregulating cyclin-dependent kinase inhibitor p27 (kip1) in a proteasome-dependent manner,²³¹ bypasses p53 inactivation in a cMyc-induced lymphomagenesis model,^{234,235} is down-regulated by c-CBL ubiquitin ligase (E3), a critical negative regulator in the BCR signal pathway,²³⁶ cooperates with Notch 1 to alter B-cell identity *in vivo*,²³⁷ activates its own promoter and Notch promoter in an EBNA-2-independent manner,²²⁴ enhances the development of autoimmune diseases in transgenic LMP-2A expression in B cells,²³⁸ induces hypersensitivity to TLR stimulation, leading to the activation of autoantigen-reactive B cells through the BCR/TLR pathway,³⁴ bypasses anergy induction in response to low levels of soluble antigen, induces NF- κ B nuclear translocation independent of BCR crosslinking²³⁹ and transactivates the human endogenous retrovirus HERV-K18 superantigen²⁴⁰ (see Table 1).

LMP-2A in epithelial cells

LMP-2A suppresses differentiation,⁷⁴ promotes epithelial cell spreading and motility together with LMP-2B,²⁴¹ leads to the transcriptional repression of the *hTERT* gene,²⁴² contributes to anoikis resistance,²⁴³ enriches cancer stem cell-like population from fibroblasts,²⁴⁴ enhances epithelial–mesenchymal transition in NPC via induction of metastatic tumor antigen (MTA1) and mammalian target of rapamycin signaling,²⁴⁵ induces the detected form of P63a (deltaP63) that impairs epithelial cell differentiation,²⁴⁶ activates DNA methyltransferase 1 leading to promoter hypermethylation of the *PTEN* gene in GC,²⁴⁷ is frequently detected in NPC and induces UDP-glucose dehydrogenase expression via ERK and PI3K/AKT pathways but not JNK and p38 pathways,²⁴⁸ 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 pathway⁶⁷ and limits the interferon together with LMP-2B by targeting interferon receptors for degradation²⁴⁹ (see Table 1).

Structure, domain and interaction

EBV encodes two nearly identical LMP-2 with the same TMs (LMP-2A and LMP-2B).²⁵⁰ 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.²⁵⁰ LMP-2A/B are constitutively expressed primarily in the plasma membrane, and also in cytoplasmic location, in all EBV-infected cells.^{250,251} LMP-2 associates with and is a substrate for a B-lymphocyte tyrosine kinase Lyn and Syk protein tyrosine kinases²⁵² 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.^{62,253} 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.²⁵⁴ 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.²²⁵ LMP-2A is secreted through exosomes similarly to LMP-1.²²² 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.²²²

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.^{255,256}

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.²⁵⁷ 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.²⁵⁸ Although EBNA-3B is dispensable for B-cell transformation, both EBNA-3A and EBNA-3C are essential.^{49,50,259} 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.^{49,50,260,261}

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.^{46,262,263}

EBNA-3C residues a.a. 130–159 bind to IRF4 or IRF8,²⁶⁴ and coactivate the EBV LMP-1 promoter with EBNA-2 through an SPI1 site in the absence of RBPJ^{258,265} (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.²⁶⁶ 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.²⁶⁶

A Bim is a cellular inducer of apoptosis. In the absence of Bim, EBNA-3A and EBNA-3C provide no survival advantage.²⁰⁵ 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.²⁶⁷

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.²⁶⁸ EBNA-3A or EBNA-3C inactivation in LCLs induces G₁ arrests resulting from EBNA-3A/C-mediated induction of *CDKN2A p16^{INK4A}* expression.^{260,261,269–272} 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.^{260,261,269,270,273} Similar to EBNA-3C, EBNA-3A interacts with many cellular partners, including PU.1, Spi-B, histone deacetylase 1, DP103, prothymosin- α , 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^{INK4A}* or *p14^{ARF}* for enabling LCL growth.²⁷⁰ EBNA-3A and EBNA-3C cooperatively repress a transcription of the *p16^{INK4A}* and *p14^{ARF}* tumor suppressors, allowing cell cycle entry²⁷⁰ (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 evasion²⁷⁴ (see Table 1).

EBV-encoded nuclear antigen-3C

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

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/D1²⁷⁷ 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;^{258,264,278–282} 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.^{264,267,273,283–287}

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.²⁸⁸ 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.^{270,272} 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,²⁶⁶ whereas EBNA-3C-mediated histone modifications are important for $p14^{ARF}$ and $p16^{INK4A}$ repression.²⁸⁹

Similar to EBNA-2 and LP, EBNA-3C regulates the viral and cellular gene transcription through interactions with cellular proteins including RBPJ^{264,265,290} 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.²⁹¹ 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.²⁷² 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.²⁷² EBNA-3C functions as a gene regulator in combination with TFs, mostly AICEs, EICEs and RUNX3.^{290–292} 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.^{293–296} The role of EBERs in EBV-induced B-lymphocyte transformation has been contradictory. Earlier reports described nonessential roles of EBER for B-lymphocyte transformation.^{48,297} However, a critical role was also demonstrated.²⁹⁸ EBER expression augments colony formation and induces growth in *in vitro* or *in vivo* tumorigenesis,^{79,299–301} resistance to RNA-dependent protein kinase (PKR)-dependent apoptosis³⁰² and cytokines including IL-10, IL-9, IGF1 and IL-6,^{303–306} and modulates innate immune response.^{307,308}

EBERs binds to La,²⁹³ PKR, ribosomal protein L22 (also called as EAP),³⁰⁹ pattern-recognition receptors, retinoic acid-inducible gene I (RIG-I), melanoma differentiation-associated gene-5³⁰⁷ and AU-rich element binding factor 1.³¹⁰ EBER-mediated RIG-I activation likely contributes to EBV oncogenesis.³⁰⁷

EBERs in complex with La release from cells³⁰⁸ and bind to the dephosphorylated PKR, which is double-stranded RNA-dependent and an interferon (IFN)-inducible serine/threonine kinase.^{311,312} Antibody to La is implicated in SLE.²⁹³ Viral infection-induced IFNs activate PKR, which phosphorylates the α -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 α result in the blockage of eukaryotic initiation factor 2 α -mediated inhibition of protein synthesis and resistance to IFN α -induced apoptosis.^{78,313,314} Most EBERs

establish stable complexes with L22 *in vivo*, thereby modulating protein translation.³¹⁵ L22 and PKR compete for EBER binding and L22 interferes with EBER inhibition of PKR and EBER-induced gene expression.³¹⁶ Interaction of EBERs with RIG-I, AU-rich element binding factor 1 and pattern-recognition receptors could activate host innate immune responses.³¹⁷ EBER double-stranded RNA structures also activate RIG-mediated NF- κ 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- κ 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.³¹⁸ 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.^{319–322}

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 BHRF1-1.³²² 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.³²³ The miR-BART2-5p targets a stress-induced natural killer cell ligand, MICB, allowing EBV-infected cells to escape recognition and subsequent elimination.^{324,325}

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*.^{326–328} In addition, BHRF1 and BART miRNAs prevent primary B cells or BLs, respectively, from apoptosis.^{327,329} In contrast, miR-BART15-3p promoted apoptosis.³³⁰ 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.³³¹ 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.^{332–336}

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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- Epstein M, Achong B, Barr Y. Virus particles in cultured lymphoblasts from Burkitt's lymphoma. *Lancet* 1964; **1**: 702–703.
- Henle G, Henle W. Immunofluorescence in cells derived from Burkitt's lymphoma. *J Bacteriol* 1966; **91**: 1248–1256.
- Henle G, Henle W. Observations on childhood infections with the Epstein-Barr virus. *J Infect Dis* 1970; **121**: 303–310.
- Henle G, Henle W, Clifford P, Diehl V, Kafuko GW, Kirya BG *et al*. Antibodies to Epstein-Barr virus in Burkitt's lymphoma and control groups. *J Natl Cancer Inst* 1969; **43**: 1147–1157.
- Henle W, Henle G. The relation of the Epstein-Barr virus to Burkitt's lymphoma. *Zentralbl Bakteriol (Orig A)* 1972; **220**: 40–46.
- Henle W, Henle G. Epstein-Barr virus-related serology in Hodgkin's disease. *Natl Cancer Inst Monogr* 1973; **36**: 79–84.
- Henle W, Henle G. Evidence for an oncogenic potential of the Epstein-Barr virus. *Cancer Res* 1973; **33**: 1419–1423.
- Henle W, Henle G. The Epstein-Barr virus (EBV) in Burkitt's lymphoma and nasopharyngeal carcinoma. *Ann Clin Lab Sci* 1974; **4**: 109–114.
- Henle W, Henle G. Epstein-Barr virus and human malignancies. *Cancer* 1974; **34**(Suppl): 1368–1374.
- Henle W, Henle G. The sero-epidemiology of Epstein-Barr virus. *Adv Pathobiol* 1976; **5**: 5–17.
- Henle W, Henle G. Evidence for an etiologic relation of the Epstein-Barr virus to human malignancies. *Laryngoscope* 1977; **87**: 467–473.
- Geser A, de The G, Lenoir G, Day NE, Williams EH. Final case reporting from the Ugandan prospective study of the relationship between EBV and Burkitt's lymphoma. *Int J Cancer* 1982; **29**: 397–400.
- Zeng Y, Zhang LG, Wu YC, Huang YS, Huang NQ, Li JY *et al*. Prospective studies on nasopharyngeal carcinoma in Epstein-Barr virus IgA/VCA antibody-positive persons in Wuzhou City, China. *Int J Cancer* 1985; **36**: 545–547.
- Sixbey JW, Vesterinen EH, Nedrud JG, Raab-Traub N, Walton LA, Pagano JS. Replication of Epstein-Barr virus in human epithelial cells infected *in vitro*. *Nature* 1983; **306**: 480–483.
- Sixbey JW, Nedrud JG, Raab-Traub N, Hanes RA, Pagano JS. Epstein-Barr virus replication in oropharyngeal epithelial cells. *N Engl J Med* 1984; **310**: 1225–1230.
- Sixbey JW, Lemon SM, Pagano JS. A second site for Epstein-Barr virus shedding: the uterine cervix. *Lancet* 1986; **2**: 1122–1124.
- Sixbey JW, Shirley P, Sloas M, Raab-Traub N, Israel V. A transformation-incompetent, nuclear antigen 2-deleted Epstein-Barr virus associated with replicative infection. *J Infect Dis* 1991; **163**: 1008–1015.

- 18 Gan YJ, Chodosh J, Morgan A, Sixbey JW. Epithelial cell polarization is a determinant in the infectious outcome of immunoglobulin A-mediated entry by Epstein-Barr virus. *J Virol* 1997; **71**: 519-526.
- 19 Pegtel DM, Middeldorp J, Thorley-Lawson DA. Epstein-Barr virus infection in *ex vivo* tonsil epithelial cell cultures of asymptomatic carriers. *J Virol* 2004; **78**: 12613-12624.
- 20 Young LS, Clark D, Sixbey JW, Rickinson AB. Epstein-Barr virus receptors on human pharyngeal epithelia. *Lancet* 1986; **1**: 240-242.
- 21 Young LS, Lau R, Rowe M, Niedobitek G, Packham G, Shanahan F *et al*. Differentiation-associated expression of the Epstein-Barr virus BZLF1 transactivator protein in oral hairy leukoplakia. *J Virol* 1991; **65**: 2868-2874.
- 22 Cruchley AT, De Souza YG, Williams DM, Greenspan D, Greenspan JS. Bromodeoxyuridine incorporation and Ki 67 expression in oral hairy leukoplakia. *Oral Dis* 1998; **4**: 9-15.
- 23 Walling DM, Clark NM, Markovitz DM, Frank TS, Braun DK, Eisenberg E *et al*. Epstein-Barr virus coinfection and recombination in non-human immunodeficiency virus-associated oral hairy leukoplakia. *J Infect Dis* 1995; **171**: 1122-1130.
- 24 Webster-Cyriaque J, Middeldorp J, Raab-Traub N. Hairy leukoplakia: an unusual combination of transforming and permissive Epstein-Barr virus infections. *J Virol* 2000; **74**: 7610-7618.
- 25 Walling DM, Ling PD, Gordadze AV, Montes-Walters M, Flaitz CM, Nichols CM. Expression of Epstein-Barr virus latent genes in oral epithelium: determinants of the pathogenesis of oral hairy leukoplakia. *J Infect Dis* 2004; **190**: 396-399.
- 26 Walling DM, Ray AJ, Nichols JE, Flaitz CM, Nichols CM. Epstein-Barr virus infection of Langerhans cell precursors as a mechanism of oral epithelial entry, persistence, and reactivation. *J Virol* 2007; **81**: 7249-7268.
- 27 Adams A, Lindahl T. Epstein-Barr virus genomes with properties of circular DNA molecules in carrier cells. *Proc Natl Acad Sci USA* 1975; **72**: 1477-1481.
- 28 Niedobitek G, Agathangelou A, Herbst H, Whitehead L, Wright DH, Young LS. Epstein-Barr virus (EBV) infection in infectious mononucleosis: virus latency, replication and phenotype of EBV-infected cells. *J Pathol* 1997; **182**: 151-159.
- 29 Niedobitek G, Kremmer E, Herbst H, Whitehead L, Dawson CW, Niedobitek E *et al*. Immunohistochemical detection of the Epstein-Barr virus-encoded latent membrane protein 2A in Hodgkin's disease and infectious mononucleosis. *Blood* 1997; **90**: 1664-1672.
- 30 Niedobitek G, Agathangelou A, Steven N, Young LS. Epstein-Barr virus (EBV) in infectious mononucleosis: detection of the virus in tonsillar B lymphocytes but not in desquamated oropharyngeal epithelial cells. *Mol Pathol* 2000; **53**: 37-42.
- 31 Kurth J, Hansmann ML, Rajewsky K, Kuppers R. Epstein-Barr virus-infected B cells expanding in germinal centers of infectious mononucleosis patients do not participate in the germinal center reaction. *Proc Natl Acad Sci USA* 2003; **100**: 4730-4735.
- 32 Souza TA, Stollar BD, Sullivan JL, Luzuriaga K, Thorley-Lawson DA. Peripheral B cells latently infected with Epstein-Barr virus display molecular hallmarks of classical antigen-selected memory B cells. *Proc Natl Acad Sci USA* 2005; **102**: 18093-18098.
- 33 Laichalk LL, Thorley-Lawson DA. Terminal differentiation into plasma cells initiates the replicative cycle of Epstein-Barr virus *in vivo*. *J Virol* 2005; **79**: 1296-1307.
- 34 Wang H, Nicholas MW, Conway KL, Sen P, Diz R, Tisch RM *et al*. EBV latent membrane protein 2A induces autoreactive B cell activation and TLR hypersensitivity. *J Immunol* 2006; **177**: 2793-2802.
- 35 Geser A, Lenoir GM, Anvret M, Bornkamm G, Klein G, Williams EH *et al*. Epstein-Barr virus markers in a series of Burkitt's lymphomas from the West Nile District, Uganda. *Eur J Cancer Clin Oncol* 1983; **19**: 1393-1404.
- 36 Henle W, Diehl V, Kohn G, Zur Hausen H, Henle G. Herpes-type virus and chromosome marker in normal leukocytes after growth with irradiated Burkitt cells. *Science* 1967; **157**: 1064-1065.
- 37 Pope J. Establishment of cell lines from peripheral leukocytes in infectious mononucleosis. *Nature* 1967; **216**: 810-811.
- 38 Pope JH, Horne MK, Scott W. Transformation of human foetal leukocytes *in vitro* by filtrates of a human leukaemic line containing herpes-like virus. *Int J Cancer* 1968; **3**: 857-866.
- 39 Alfieri C, Birkenbach M, Kieff E. Early events in Epstein-Barr virus infection of human B lymphocytes. *Virology* 1991; **181**: 595-608.
- 40 Cohen JI, Wang F, Kieff E. Epstein-Barr virus nuclear protein 2 mutations define essential domains for transformation and transactivation. *J Virol* 1991; **65**: 2545-2554.
- 41 Cohen JI, Wang F, Mannick J, Kieff E. Epstein-Barr virus nuclear protein 2 is a key determinant of lymphocyte transformation. *Proc Natl Acad Sci USA* 1989; **86**: 9558-9562.
- 42 Mannick JB, Cohen JI, Birkenbach M, Marchini A, Kieff E. The Epstein-Barr virus nuclear protein encoded by the leader of the EBNA RNAs is important in B-lymphocyte transformation. *J Virol* 1991; **65**: 6826-6837.
- 43 Longnecker R, Miller CL, Miao XQ, Tomkinson B, Kieff E. The last seven transmembrane and carboxy-terminal cytoplasmic domains of Epstein-Barr virus latent membrane protein 2 (LMP2) are dispensable for lymphocyte infection and growth transformation *in vitro*. *J Virol* 1993; **67**: 2006-2013.
- 44 Longnecker R, Miller CL, Tomkinson B, Miao XQ, Kieff E. Deletion of DNA encoding the first five transmembrane domains of Epstein-Barr virus latent membrane proteins 2A and 2B. *J Virol* 1993; **67**: 5068-5074.
- 45 Marchini A, Tomkinson B, Cohen JI, Kieff E. BHRF1, the Epstein-Barr virus gene with homology to Bc12, is dispensable for B-lymphocyte transformation and virus replication. *J Virol* 1991; **65**: 5991-6000.
- 46 Robertson ES, Grossman S, Johannsen E, Miller C, Lin J, Tomkinson B *et al*. Epstein-Barr virus nuclear protein 3C modulates transcription through interaction with the sequence-specific DNA-binding protein J kappa. *J Virol* 1995; **69**: 3108-3116.
- 47 Robertson ES, Tomkinson B, Kieff E. An Epstein-Barr virus with a 58-kilobase-pair deletion that includes BARFO transforms B lymphocytes *in vitro*. *J Virol* 1994; **68**: 1449-1458.
- 48 Swaminathan S, Tomkinson B, Kieff E. Recombinant Epstein-Barr virus with small RNA (EBER) genes deleted transforms lymphocytes and replicates *in vitro*. *Proc Natl Acad Sci USA* 1991; **88**: 1546-1550.
- 49 Tomkinson B, Kieff E. Use of second-site homologous recombination to demonstrate that Epstein-Barr virus nuclear protein 3B is not important for lymphocyte infection or growth transformation *in vitro*. *J Virol* 1992; **66**: 2893-2903.
- 50 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**: 2014-2025.
- 51 Kaye KM, Izumi KM, Kieff E. Epstein-Barr virus latent membrane protein 1 is essential for B-lymphocyte growth transformation. *Proc Natl Acad Sci USA* 1993; **90**: 9150-9154.
- 52 Kaye KM, Izumi KM, Li H, Johannsen E, Davidson D, Longnecker R *et al*. An Epstein-Barr virus that expresses only the first 231 LMP1 amino acids efficiently initiates primary B-lymphocyte growth transformation. *J Virol* 1999; **73**: 10525-10530.
- 53 Kaye KM, Izumi KM, Mosialos G, Kieff E. The Epstein-Barr virus LMP1 cytoplasmic carboxy terminus is essential for B-lymphocyte transformation; fibroblast cocultivation complements a critical function within the terminal 155 residues. *J Virol* 1995; **69**: 675-683.
- 54 Izumi KM, Cahir McFarland ED, Riley EA, Rizzo D, Chen Y, Kieff E. The residues between the two transformation effector sites of Epstein-Barr virus latent membrane protein 1 are not critical for B-lymphocyte growth transformation. *J Virol* 1999; **73**: 9908-9916.
- 55 Izumi KM, Cahir McFarland ED, Ting AT, Riley EA, Seed B, Kieff ED. The Epstein-Barr virus oncoprotein latent membrane protein 1 engages the tumor necrosis factor receptor-associated proteins TRADD and receptor-interacting protein (RIP) but does not induce apoptosis or require RIP for NF-kappaB activation. *Mol Cell Biol* 1999; **19**: 5759-5767.
- 56 Izumi KM, Kaye KM, Kieff ED. Epstein-Barr virus recombinant molecular genetic analysis of the LMP1 amino-terminal cytoplasmic domain reveals a probable structural role, with no component essential for primary B-lymphocyte growth transformation. *J Virol* 1994; **68**: 4369-4376.
- 57 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 USA* 1997; **94**: 1447-1452.
- 58 Izumi KM, Kieff ED. The Epstein-Barr virus oncogene product latent membrane protein 1 engages the tumor necrosis factor receptor-associated death domain protein to mediate B lymphocyte growth transformation and activate NF-kappaB. *Proc Natl Acad Sci USA* 1997; **94**: 12592-12597.
- 59 Cahir-McFarland ED, Carter K, Rosenwald A, Giltman JM, Henrickson SE, Staudt LM *et al*. Role of NF-kappa B in cell survival and transcription of

- latent membrane protein 1-expressing or Epstein–Barr virus latency III-infected cells. *J Virol* 2004; **78**: 4108–4119.
- 60 Cahir-McFarland ED, Davidson DM, Schauer SL, Duong J, Kieff E. NF-kappa B inhibition causes spontaneous apoptosis in Epstein–Barr virus-transformed lymphoblastoid cells. *Proc Natl Acad Sci USA* 2000; **97**: 6055–6060.
 - 61 Teramoto N, Maeda A, Kobayashi K, Hayashi K, Oka T, Takahashi K *et al*. Epstein–Barr virus infection to Epstein–Barr virus-negative nasopharyngeal carcinoma cell line TW03 enhances its tumorigenicity. *Lab Invest* 2000; **80**: 303–312.
 - 62 Miller CL, Burkhardt AL, Lee JH, Stealey B, Longnecker R, Bolen JB *et al*. Integral membrane protein 2 of Epstein–Barr virus regulates reactivation from latency through dominant negative effects on protein-tyrosine kinases. *Immunity* 1995; **2**: 155–166.
 - 63 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**: 405–411.
 - 64 Caldwell RG, Brown RC, Longnecker R. Epstein–Barr virus LMP2A-induced B-cell survival in two unique classes of EmuLMP2A transgenic mice. *J Virol* 2000; **74**: 1101–1113.
 - 65 Swart R, Ruf IK, Sample J, Longnecker R. Latent membrane protein 2A-mediated effects on the phosphatidylinositol 3-kinase/Akt pathway. *J Virol* 2000; **74**: 10838–10845.
 - 66 Engels N, Merchant M, Pappu R, Chan AC, Longnecker R, Wienands J. Epstein–Barr virus latent membrane protein 2A (LMP2A) employs the SLP-65 signaling module. *J Exp Med* 2001; **194**: 255–264.
 - 67 Fukuda M, Longnecker R. Epstein–Barr virus latent membrane protein 2A mediates transformation through constitutive activation of the Ras/PI3-K/Akt pathway. *J Virol* 2007; **81**: 9299–9306.
 - 68 Pathmanathan R, Prasad U, Sadler R, Flynn K, Raab-Traub N. Clonal proliferations of cells infected with Epstein–Barr virus in preinvasive lesions related to nasopharyngeal carcinoma. *N Engl J Med* 1995; **333**: 693–698.
 - 69 Fries KL, Miller WE, Raab-Traub N. Epstein–Barr virus latent membrane protein 1 blocks p53-mediated apoptosis through the induction of the A20 gene. *J Virol* 1996; **70**: 8653–8659.
 - 70 Miller WE, Mosialos G, Kieff E, Raab-Traub N. Epstein–Barr virus LMP1 induction of the epidermal growth factor receptor is mediated through a TRAF signaling pathway distinct from NF-kappaB activation. *J Virol* 1997; **71**: 586–594.
 - 71 Scholle F, Bendt KM, Raab-Traub N. Epstein–Barr virus LMP2A transforms epithelial cells, inhibits cell differentiation, and activates Akt. *J Virol* 2000; **74**: 10681–10689.
 - 72 Morrison JA, Klingelutz AJ, Raab-Traub N. Epstein–Barr virus latent membrane protein 2A activates beta-catenin signaling in epithelial cells. *J Virol* 2003; **77**: 12276–12284.
 - 73 Everly Jr DN, Mainou BA, Raab-Traub N. Induction of Id1 and Id3 by latent membrane protein 1 of Epstein–Barr virus and regulation of p27/Kip and cyclin-dependent kinase 2 in rodent fibroblast transformation. *J Virol* 2004; **78**: 13470–13478.
 - 74 Morrison JA, Raab-Traub N. Roles of the ITAM and PY motifs of Epstein–Barr virus latent membrane protein 2A in the inhibition of epithelial cell differentiation and activation of {beta}-catenin signaling. *J Virol* 2005; **79**: 2375–2382.
 - 75 Thornburg NJ, Raab-Traub N. Induction of EGFR expression by EBV LMP1 CTAR1 is mediated by NF-(kappa)B p50 homodimer/BCL-3 complexes. *J Virol* 2007; **81**: 12954–12961.
 - 76 Komano J, Takada K. Role of bcl-2 in Epstein–Barr virus-induced malignant conversion of Burkitt's lymphoma cell line Akata. *J Virol* 2001; **75**: 1561–1564.
 - 77 Maruo S, Nanbo A, Takada K. Replacement of the Epstein–Barr virus plasmid with the EBV plasmid in Burkitt's lymphoma cells. *J Virol* 2001; **75**: 9977–9982.
 - 78 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**: 954–965.
 - 79 Ruf IK, Rhyne PW, Yang C, Cleveland JL, Sample JT. Epstein–Barr virus small RNAs potentiate tumorigenicity of Burkitt lymphoma cells independently of an effect on apoptosis. *J Virol* 2000; **74**: 10223–10228.
 - 80 Reisman D, Yates J, Sugden B. A putative origin of replication of plasmids derived from Epstein–Barr virus is composed of two cis-acting components. *Mol Cell Biol* 1985; **5**: 1822–1832.
 - 81 Sugden B, Marsh K, Yates J. A vector that replicates as a plasmid and can be efficiently selected in B-lymphoblasts transformed by Epstein–Barr virus. *Mol Cell Biol* 1985; **5**: 410–413.
 - 82 Yates J, Warren N, Reisman D, Sugden B. A cis-acting element from the Epstein–Barr viral genome that permits stable replication of recombinant plasmids in latently infected cells. *Proc Natl Acad Sci USA* 1984; **81**: 3806–3810.
 - 83 Yates JL, Warren N, Sugden B. Stable replication of plasmids derived from Epstein–Barr virus in various mammalian cells. *Nature* 1985; **313**: 812–815.
 - 84 Malik-Soni N, Frappier L. Nucleophosmin contributes to the transcriptional activation function of the Epstein–Barr virus EBNA1 protein. *J Virol* 2014; **88**: 2323–2326.
 - 85 Liu CD, Chen YL, Min YL, Zhao B, Cheng CP, Kang MS *et al*. The nuclear chaperone nucleophosmin escorts an Epstein–Barr virus nuclear antigen to establish transcriptional cascades for latent infection in human B cells. *PLoS Pathogen* 2012; **8**: e1003084.
 - 86 Sivachandran N, Wang X, Frappier L. Functions of the Epstein–Barr virus EBNA1 protein in viral reactivation and lytic infection. *J Virol* 2012; **86**: 6146–6158.
 - 87 Mansouri S, Pan Q, Blencowe BJ, Claycomb JM, Frappier L. Epstein–Barr virus EBNA1 protein regulates viral latency through effects on let-7 microRNA and dicer. *J Virol* 2014; **88**: 11166–11177.
 - 88 Sivachandran N, Sarkari F, Frappier L. Epstein–Barr nuclear antigen 1 contributes to nasopharyngeal carcinoma through disruption of PML nuclear bodies. *PLoS Pathogen* 2008; **4**: e1000170.
 - 89 Canaan A, Haviv I, Urban AE, Schulz VP, Hartman S, Zhang Z *et al*. EBNA1 regulates cellular gene expression by binding cellular promoters. *Proc Natl Acad Sci USA* 2009; **106**: 22421–22426.
 - 90 Dresang LR, Vereide DT, Sugden B. Identifying sites bound by Epstein–Barr virus nuclear antigen 1 (EBNA1) in the human genome: defining a position-weighted matrix to predict sites bound by EBNA1 in viral genomes. *J Virol* 2009; **83**: 2930–2940.
 - 91 Sugden B, Warren N. A promoter of Epstein–Barr virus that can function during latent infection can be transactivated by EBNA-1, a viral protein required for viral DNA replication during latent infection. *J Virol* 1989; **63**: 2644–2649.
 - 92 Wood VH, O'Neil JD, Wei W, Stewart SE, Dawson CW, Young LS. Epstein–Barr virus-encoded EBNA1 regulates cellular gene transcription and modulates the STAT1 and TGFbeta signaling pathways. *Oncogene* 2007; **26**: 4135–4147.
 - 93 Flavell JR, Baumforth KR, Wood VH, Davies GL, Wei W, Reynolds GM *et al*. Down-regulation of the TGF-beta target gene, PTPRK, by the Epstein–Barr virus encoded EBNA1 contributes to the growth and survival of Hodgkin lymphoma cells. *Blood* 2008; **111**: 292–301.
 - 94 Baumforth KR, Birgersdotter A, Reynolds GM, Wei W, Kapatai G, Flavell JR *et al*. Expression of the Epstein–Barr virus-encoded Epstein–Barr virus nuclear antigen 1 in Hodgkin's lymphoma cells mediates up-regulation of CCL20 and the migration of regulatory T cells. *Am J Pathol* 2008; **173**: 195–204.
 - 95 Valentine R, Dawson CW, Hu C, Shah KM, Owen TJ, Date KL *et al*. Epstein–Barr virus-encoded EBNA1 inhibits the canonical NF-kappaB pathway in carcinoma cells by inhibiting IKK phosphorylation. *Mol Cancer* 2010; **9**: 1.
 - 96 O'Neil JD, Owen TJ, Wood VH, Date KL, Valentine R, Chukwuma MB *et al*. Epstein–Barr virus-encoded EBNA1 modulates the AP-1 transcription factor pathway in nasopharyngeal carcinoma cells and enhances angiogenesis in vitro. *J Gen Virol* 2008; **89**: 2833–2842.
 - 97 Baer R, Bankier AT, Biggin MD, Deininger PL, Farrell PJ, Gibson TJ *et al*. DNA sequence and expression of the B95-8 Epstein–Barr virus genome. *Nature* 1984; **310**: 207–211.
 - 98 Yates JL, Camiolo SM. Dissection of DNA replication and enhancer activation function of Epstein–Barr virus nuclear antigen 1. *Cancer Cells* 1988; **6**: 197–205.
 - 99 Ambinder RF, Mullen MA, Chang YN, Hayward GS, Hayward SD. Functional domains of Epstein–Barr virus nuclear antigen EBNA-1. *J Virol* 1991; **65**: 1466–1478.
 - 100 Shah WA, Ambinder RF, Hayward GS, Hayward SD. Binding of EBNA-1 to DNA creates a protease-resistant domain that encompasses the DNA recognition and dimerization functions. *J Virol* 1992; **66**: 3355–3362.
 - 101 Goldsmith K, Bendell L, Frappier L. Identification of EBNA1 amino acid sequences required for the interaction of the functional elements of the Epstein–Barr virus latent origin of DNA replication. *J Virol* 1993; **67**: 3418–3426.

- 102 Frappier L, Goldsmith K, Bendell L. Stabilization of the EBNA1 protein on the Epstein-Barr virus latent origin of DNA replication by a DNA looping mechanism. *J Biol Chem* 1994; **269**: 1057–1062.
- 103 Bochkarev A, Barwell JA, Pfuetzner RA, Furey W Jr, Edwards AM, Frappier L. Crystal structure of the DNA-binding domain of the Epstein-Barr virus origin-binding protein EBNA 1. *Cell* 1995; **83**: 39–46.
- 104 Bochkarev A, Barwell JA, Pfuetzner RA, Bochkareva E, Frappier L, Edwards AM. Crystal structure of the DNA-binding domain of the Epstein-Barr virus origin-binding protein, EBNA1, bound to DNA. *Cell* 1996; **84**: 791–800.
- 105 Summers H, Barwell JA, Pfuetzner RA, Edwards AM, Frappier L. Cooperative assembly of EBNA1 on the Epstein-Barr virus latent origin of replication. *J Virol* 1996; **70**: 1228–1231.
- 106 Bochkarev A, Bochkareva E, Frappier L, Edwards AM. The 2.2A structure of a permanganate-sensitive DNA site bound by the Epstein-Barr virus origin binding protein, EBNA1. *J Mol Biol* 1998; **284**: 1273–1278.
- 107 Heller M, Flemington E, Kieff E, Deininger P. Repeat arrays in cellular DNA related to the Epstein-Barr virus IR3 repeat. *Mol Cell Biol* 1985; **5**: 457–465.
- 108 Heller M, Henderson A, Ripley S, Van Santen V, Kieff E. The IR3 repeat in Epstein-Barr virus DNA has homology to cell DNA, encodes part of a messenger RNA in EBV transformed cells but does not mediate integration of Epstein-Barr virus DNA. In: Prasad U *et al.* (eds) *Nasopharyngeal Carcinoma: Current Concepts*. University of Malaya: Kuala Lumpur, 1983, pp 177–202.
- 109 Heller M, van Santen V, Kieff E. Simple repeat sequence in Epstein-Barr virus DNA is transcribed in latent and productive infections. *J Virol* 1982; **44**: 311–320.
- 110 Yin Y, Manoury B, Fahraeus R. Self-inhibition of synthesis and antigen presentation by Epstein-Barr virus-encoded EBNA1. *Science* 2003; **301**: 1371–1374.
- 111 Trivedi P, Masucci MG, Winberg G, Klein G. The Epstein-Barr-virus-encoded membrane protein LMP but not the nuclear antigen EBNA-1 induces rejection of transfected murine mammary carcinoma cells. *Int J Cancer* 1991; **48**: 794–800.
- 112 Levitskaya J, Coram M, Levitsky V, Imreh S, Steigerwald-Mullen PM, Klein G *et al.* Inhibition of antigen processing by the internal repeat region of the Epstein-Barr virus nuclear antigen-1. *Nature* 1995; **375**: 685–688.
- 113 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 USA* 1997; **94**: 12616–12621.
- 114 Sharipo A, Imreh M, Leonchiks A, Imreh S, Masucci MG. A minimal glycine-alanine repeat prevents the interaction of ubiquitinated I kappaB alpha with the proteasome: a new mechanism for selective inhibition of proteolysis. *Nat Med* 1998; **4**: 939–944.
- 115 Dantuma NP, Heessen S, Lindsten K, Jellne M, Masucci MG. Inhibition of proteasomal degradation by the gly-Ala repeat of Epstein-Barr virus is influenced by the length of the repeat and the strength of the degradation signal. *Proc Natl Acad Sci USA* 2000; **97**: 8381–8385.
- 116 Dantuma NP, Sharipo A, Masucci MG. Avoiding proteasomal processing: the case of EBNA1. *Curr Top Microbiol Immunol* 2002; **269**: 23–36.
- 117 Fogg MH, Kaur A, Cho YG, Wang F. The CD8+ T-cell response to an Epstein-Barr virus-related gammaherpesvirus infecting rhesus macaques provides evidence for immune evasion by the EBNA-1 homologue. *J Virol* 2005; **79**: 12681–12691.
- 118 Bashaw JM, Yates JL. Replication from oriP of Epstein-Barr virus requires exact spacing of two bound dimers of EBNA1 which bend DNA. *J Virol* 2001; **75**: 10603–10611.
- 119 Hung SC, Kang MS, Kieff E. Maintenance of Epstein-Barr virus (EBV) oriP-based episomes requires EBV-encoded nuclear antigen-1 chromosome-binding domains, which can be replaced by high-mobility group-I or histone H1. *Proc Natl Acad Sci USA* 2001; **98**: 1865–1870.
- 120 Middleton T, Sugden B. EBNA1 can link the enhancer element to the initiator element of the Epstein-Barr virus plasmid origin of DNA replication. *J Virol* 1992; **66**: 489–495.
- 121 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**: 4067–4071.
- 122 Rawlins DR, Milman G, Hayward SD, Hayward GS. Sequence-specific DNA binding of the Epstein-Barr virus nuclear antigen (EBNA-1) to clustered sites in the plasmid maintenance region. *Cell* 1985; **42**: 859–868.
- 123 Yates JL, Camiolo SM, Bashaw JM. The minimal replicator of Epstein-Barr virus oriP. *J Virol* 2000; **74**: 4512–4522.
- 124 Kitamura R, Sekimoto T, Ito S, Harada S, Yamagata H, Masai H *et al.* Nuclear import of Epstein-Barr virus nuclear antigen 1 mediated by NPI-1 (Importin alpha5) is up- and down-regulated by phosphorylation of the nuclear localization signal for which Lys379 and Arg380 are essential. *J Virol* 2006; **80**: 1979–1991.
- 125 Kang MS, Hung SC, Kieff E. Epstein-Barr virus nuclear antigen 1 activates transcription from episomal but not integrated DNA and does not alter lymphocyte growth. *Proc Natl Acad Sci USA* 2001; **98**: 15233–15238.
- 126 Yin Q, Flemington EK. siRNAs against the Epstein-Barr virus latency replication factor, EBNA1, inhibit its function and growth of EBV-dependent tumor cells. *Virology* 2006; **346**: 385–393.
- 127 Nasimuzzaman M, Kuroda M, Dohno S, Yamamoto T, Iwatsuki K, Matsuzaki S *et al.* Eradication of Epstein-Barr virus episome and associated inhibition of infected tumor cell growth by adenovirus vector-mediated transduction of dominant-negative EBNA1. *Mol Ther* 2005; **11**: 578–590.
- 128 Ceccarelli DF, Frappier L. Functional analyses of the EBNA1 origin DNA binding protein of Epstein-Barr virus. *J Virol* 2000; **74**: 4939–4948.
- 129 Kirchmaier AL, Sugden B. Dominant-negative inhibitors of EBNA-1 of Epstein-Barr virus. *J Virol* 1997; **71**: 1766–1775.
- 130 Wu H, Kapoor P, Frappier L. Separation of the DNA replication, segregation, and transcriptional activation functions of Epstein-Barr nuclear antigen 1. *J Virol* 2002; **76**: 2480–2490.
- 131 Lupton S, Levine AJ. Mapping genetic elements of Epstein-Barr virus that facilitate extrachromosomal persistence of Epstein-Barr virus-derived plasmids in human cells. *Mol Cell Biol* 1985; **5**: 2533–2542.
- 132 Jones CH, Hayward SD, Rawlins DR. Interaction of the lymphocyte-derived Epstein-Barr virus nuclear antigen EBNA-1 with its DNA-binding sites. *J Virol* 1989; **63**: 101–110.
- 133 Hampar B, Tanaka A, Nonoyama M, Derge JG. Replication of the resident repressed Epstein-Barr virus genome during the early S phase (S-1 period) of nonproducer Raji cells. *Proc Natl Acad Sci USA* 1974; **71**: 631–633.
- 134 Adams A. Replication of latent Epstein-Barr virus genomes in Raji cells. *J Virol* 1987; **61**: 1743–1746.
- 135 Lindahl T, Adams A, Bjursell G, Bornkamm GW, Kaschka-Dierich C, Jehn U. Covalently closed circular duplex DNA of Epstein-Barr virus in a human lymphoid cell line. *J Mol Biol* 1976; **102**: 511–530.
- 136 Nonoyama M, Pagano JS. Replication of viral deoxyribonucleic acid and breakdown of cellular deoxyribonucleic acid in Epstein-Barr virus infection. *J Virol* 1972; **9**: 714–716.
- 137 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**: 483–488.
- 138 Sugden B, Warren N. Plasmid origin of replication of Epstein-Barr virus, oriP, does not limit replication in cis. *Mol Biol Med* 1988; **5**: 85–94.
- 139 Kirchmaier AL, Sugden B. Plasmid maintenance of derivatives of oriP of Epstein-Barr virus. *J Virol* 1995; **69**: 1280–1283.
- 140 Hudson GS, Gibson TJ, Barrell BG. The BamHI F region of the B95-8 Epstein-Barr virus genome. *Virology* 1985; **147**: 99–109.
- 141 Reisman D, Sugden B. trans activation of an Epstein-Barr viral transcriptional enhancer by the Epstein-Barr viral nuclear antigen 1. *Mol Cell Biol* 1986; **6**: 3838–3846.
- 142 Wysokenski DA, Yates JL. Multiple EBNA1-binding sites are required to form an EBNA1-dependent enhancer and to activate a minimal replicative origin within oriP of Epstein-Barr virus. *J Virol* 1989; **63**: 2657–2666.
- 143 Gahn TA, Sugden B. An EBNA-1-dependent enhancer acts from a distance of 10 kilobase pairs to increase expression of the Epstein-Barr virus LMP gene. *J Virol* 1995; **69**: 2633–2636.
- 144 Puglielli MT, Woisetschlaeger M, Speck SH. OriP is essential for EBNA gene promoter activity in Epstein-Barr virus-immortalized lymphoblastoid cell lines. *J Virol* 1996; **70**: 5758–5768.
- 145 Aiyar A, Tyree C, Sugden B. The plasmid replicon of EBV consists of multiple cis-acting elements that facilitate DNA synthesis by the cell and a viral maintenance element. *EMBO J* 1998; **17**: 6394–6403.
- 146 Shire K, Ceccarelli DF, Avolio-Hunter TM, Frappier L. EBP2, a human protein that interacts with sequences of the Epstein-Barr virus nuclear antigen 1 important for plasmid maintenance. *J Virol* 1999; **73**: 2587–2595.

- 147 Fischer N, Kremmer E, Lautscham G, Mueller-Lantzsch N, Grasser FA. Epstein-Barr virus nuclear antigen 1 forms a complex with the nuclear transporter karyopherin alpha2. *J Biol Chem* 1997; **272**: 3999-4005.
- 148 Holowaty MN, Zeghouf M, Wu H, Tellam J, Athanasopoulos V, Greenblatt J *et al*. Protein profiling with Epstein-Barr nuclear antigen-1 reveals an interaction with the herpesvirus-associated ubiquitin-specific protease HAUSP/USP7. *J Biol Chem* 2003; **278**: 29987-29994.
- 149 Kim AL, Maher M, Hayman JB, Ozer J, Zerby D, Yates JL *et al*. An imperfect correlation between DNA replication activity of Epstein-Barr virus nuclear antigen 1 (EBNA1) and binding to the nuclear import receptor, Rch1/importin alpha. *Virology* 1997; **239**: 340-351.
- 150 Van Scoy S, Watakabe I, Krainer AR, Hearing J. Human p32: a coactivator for Epstein-Barr virus nuclear antigen-1-mediated transcriptional activation and possible role in viral latent cycle DNA replication. *Virology* 2000; **275**: 145-157.
- 151 Wang Y, Finan JE, Middeldorp JM, Hayward SD. P32/TAP, a cellular protein that interacts with EBNA-1 of Epstein-Barr virus. *Virology* 1997; **236**: 18-29.
- 152 Shire K, Kapoor P, Jiang K, Hing MN, Sivachandran N, Nguyen T *et al*. Regulation of the EBNA1 Epstein-Barr virus protein by serine phosphorylation and arginine methylation. *J Virol* 2006; **80**: 5261-5272.
- 153 Sarkari F, Sanchez-Alcaraz T, Wang S, Holowaty MN, Sheng Y, Frappier L. EBNA1-mediated recruitment of a histone H2B deubiquitylating complex to the Epstein-Barr virus latent origin of DNA replication. *PLoS Pathogen* 2009; **5**: e1000624.
- 154 Sarkari F, Wang X, Nguyen T, Frappier L. The herpesvirus associated ubiquitin specific protease, USP7, is a negative regulator of PML proteins and PML nuclear bodies. *PLoS One* 2011; **6**: e16598.
- 155 Sivachandran N, Cao JY, Frappier L. Epstein-Barr virus nuclear antigen 1 Hijacks the host kinase CK2 to disrupt PML nuclear bodies. *J Virol* 2010; **84**: 11113-11123.
- 156 Malik-Soni N, Frappier L. Proteomic profiling of EBNA1-host protein interactions in latent and lytic Epstein-Barr virus infections. *J Virol* 2012; **86**: 6999-7002.
- 157 Murray RJ, Wang D, Young LS, Wang F, Rowe M, Kieff E *et al*. Epstein-Barr virus-specific cytotoxic T-cell recognition of transfectants expressing the virus-coded latent membrane protein LMP. *J Virol* 1988; **62**: 3747-3755.
- 158 Portal D, Zhao B, Calderwood MA, Sommermann T, Johannsen E, Kieff E. EBV nuclear antigen EBNA1P dismisses transcription repressors NCoR and RBPJ from enhancers and EBNA2 increases NCoR-deficient RBPJ DNA binding. *Proc Natl Acad Sci USA* 2011; **108**: 7808-7813.
- 159 Peng R, Moses SC, Tan J, Kremmer E, Ling PD. The Epstein-Barr virus EBNA-LP protein preferentially coactivates EBNA2-mediated stimulation of latent membrane proteins expressed from the viral divergent promoter. *J Virol* 2005; **79**: 4492-4505.
- 160 Portal D, Zhou H, Zhao B, Kharchenko PV, Lowry E, Wong L *et al*. Epstein-Barr virus nuclear antigen leader protein localizes to promoters and enhancers with cell transcription factors and EBNA2. *Proc Natl Acad Sci USA* 2013; **110**: 18537-18542.
- 161 Zhao B, Zou J, Wang H, Johannsen E, Peng CW, Quackenbush J *et al*. Epstein-Barr virus exploits intrinsic B-lymphocyte transcription programs to achieve immortal cell growth. *Proc Natl Acad Sci USA* 2011; **108**: 14902-14907.
- 162 Merkenschlager M, Odom DT. CTCF and cohesin: linking gene regulatory elements with their targets. *Cell* 2013; **152**: 1285-1297.
- 163 Harada S, Kieff E. Epstein-Barr virus nuclear protein LP stimulates EBNA-2 acidic domain-mediated transcriptional activation. *J Virol* 1997; **71**: 6611-6618.
- 164 Han I, Harada S, Weaver D, Xue Y, Lane W, Orstavik S *et al*. EBNA-LP associates with cellular proteins including DNA-PK and HA95. *J Virol* 2001; **75**: 2475-2481.
- 165 Mannick JB, Tong X, Hemnes A, Kieff E. The Epstein-Barr virus nuclear antigen leader protein associates with hsp72/hsc73. *J Virol* 1995; **69**: 8169-8172.
- 166 Portal D, Rosendorff A, Kieff E. Epstein-Barr nuclear antigen leader protein coactivates transcription through interaction with histone deacetylase 4. *Proc Natl Acad Sci USA* 2006; **103**: 19278-19283.
- 167 Peng CW, Xue Y, Zhao B, Johannsen E, Kieff E, Harada S. Direct interactions between Epstein-Barr virus leader protein LP and the EBNA2 acidic domain underlie coordinate transcriptional regulation. *Proc Natl Acad Sci USA* 2004; **101**: 1033-1038.
- 168 Henkel T, Ling PD, Hayward SD, Peterson MG. Mediation of Epstein-Barr virus EBNA2 transactivation by recombination signal-binding protein J kappa. *Science* 1994; **265**: 92-95.
- 169 Tong X, Drapkin R, Yalamanchili R, Mosialos G, Kieff E. The Epstein-Barr virus nuclear protein 2 acidic domain forms a complex with a novel cellular coactivator that can interact with TFIIE. *Mol Cell Biol* 1995; **15**: 4735-4744.
- 170 Tong X, Wang F, Thut CJ, Kieff E. The Epstein-Barr virus nuclear protein 2 acidic domain can interact with TFIIB, TAF40, and RPA70 but not with TATA-binding protein. *J Virol* 1995; **69**: 585-588.
- 171 Mancao C, Altmann M, Jungnickel B, Hammerschmidt W. Rescue of 'crippled' germinal center B cells from apoptosis by Epstein-Barr virus. *Blood* 2005; **106**: 4339-4344.
- 172 Mosialos G, Birkenbach M, Yalamanchili R, VanArsdale T, Ware C, Kieff E. The Epstein-Barr virus transforming protein LMP1 engages signaling proteins for the tumor necrosis factor receptor family. *Cell* 1995; **80**: 389-399.
- 173 Wang D, Liebowitz D, Kieff E. An EBV membrane protein expressed in immortalized lymphocytes transforms established rodent cells. *Cell* 1985; **43**: 831-840.
- 174 Wang D, Liebowitz D, Kieff E. The truncated form of the Epstein-Barr virus latent-infection membrane protein expressed in virus replication does not transform rodent fibroblasts. *J Virol* 1988; **62**: 2337-2346.
- 175 Baichwal VR, Sugden B. Transformation of Balb 3T3 cells by the BNLF-1 gene of Epstein-Barr virus. *Oncogene* 1988; **2**: 461-467.
- 176 Moorthy RK, Thorley-Lawson DA. All three domains of the Epstein-Barr virus-encoded latent membrane protein LMP-1 are required for transformation of rat-1 fibroblasts. *J Virol* 1993; **67**: 1638-1646.
- 177 Hu LF, Chen F, Zheng X, Ernberg I, Cao SL, Christensson B *et al*. Clonability and tumorigenicity of human epithelial cells expressing the EBV encoded membrane protein LMP1. *Oncogene* 1993; **8**: 1575-1583.
- 178 Kondo S, Wakisaka N, Schell MJ, Horikawa T, Sheen TS, Sato H *et al*. Epstein-Barr virus latent membrane protein 1 induces the matrix metalloproteinase-1 promoter via an Ets binding site formed by a single nucleotide polymorphism: enhanced susceptibility to nasopharyngeal carcinoma. *Int J Cancer* 2005; **115**: 368-376.
- 179 Wakisaka N, Pagano JS. Epstein-Barr virus induces invasion and metastasis factors. *Anticancer Res* 2003; **23**: 2133-2138.
- 180 Lo AK, Liu Y, Wang XH, Huang DP, Yuen PW, Wong YC *et al*. Alterations of biologic properties and gene expression in nasopharyngeal epithelial cells by the Epstein-Barr virus-encoded latent membrane protein 1. *Lab Invest* 2003; **83**: 697-709.
- 181 Kim KR, Yoshizaki T, Miyamori H, Hasegawa K, Horikawa T, Furukawa M *et al*. Transformation of Madin-Darby canine kidney (MDCK) epithelial cells by Epstein-Barr virus latent membrane protein 1 (LMP1) induces expression of Ets1 and invasive growth. *Oncogene* 2000; **19**: 1764-1771.
- 182 Nicholson LJ, Hopwood P, Johannessen I, Salisbury JR, Codd J, Thorley-Lawson D *et al*. Epstein-Barr virus latent membrane protein does not inhibit differentiation and induces tumorigenicity of human epithelial cells. *Oncogene* 1997; **15**: 275-283.
- 183 Sheu LF, Chen A, Meng CL, Ho KC, Lee WH, Leu FJ *et al*. Enhanced malignant progression of nasopharyngeal carcinoma cells mediated by the expression of Epstein-Barr nuclear antigen 1 *in vivo*. *J Pathol* 1996; **180**: 243-248.
- 184 Miller WE, Earp HS, Raab-Traub N. The Epstein-Barr virus latent membrane protein 1 induces expression of the epidermal growth factor receptor. *J Virol* 1995; **69**: 4390-4398.
- 185 Niedobitek G, Fahraeus R, Herbst H, Latza U, Ferszt A, Klein G *et al*. The Epstein-Barr virus encoded membrane protein (LMP) induces phenotypic changes in epithelial cells. *Virchows Arch B* 1992; **62**: 55-59.
- 186 Dawson CW, Rickinson AB, Young LS. Epstein-Barr virus latent membrane protein inhibits human epithelial cell differentiation. *Nature* 1990; **344**: 777-780.
- 187 Fahraeus R, Rymo L, Rhim JS, Klein G. Morphological transformation of human keratinocytes expressing the LMP gene of Epstein-Barr virus. *Nature* 1990; **345**: 447-449.
- 188 Carter KL, Cahir-McFarland E, Kieff E. Epstein-Barr virus-induced changes in B-lymphocyte gene expression. *J Virol* 2002; **76**: 10427-10436.
- 189 Birkenbach M, Josefsen K, Yalamanchili R, Lenoir G, Kieff E. Epstein-Barr virus-induced genes: first lymphocyte-specific G protein-coupled peptide receptors. *J Virol* 1993; **67**: 2209-2220.

- 190 Birkenbach M, Liebowitz D, Wang F, Sample J, Kieff E. Epstein-Barr virus latent infection membrane protein increases vimentin expression in human B-cell lines. *J Virol* 1989; **63**: 4079-4084.
- 191 Henderson S, Rowe M, Gregory C, Croom-Carter D, Wang F, Longnecker R *et al*. Induction of bcl-2 expression by Epstein-Barr virus latent membrane protein 1 protects infected B cells from programmed cell death. *Cell* 1991; **65**: 1107-1115.
- 192 Laherty CD, Hu HM, Oipari 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**: 24157-24160.
- 193 Liebowitz D, Kieff E. Epstein-Barr virus latent membrane protein: induction of B-cell activation antigens and membrane patch formation does not require vimentin. *J Virol* 1989; **63**: 4051-4054.
- 194 Martin JM, Veis D, Korsmeyer SJ, Sugden B. Latent membrane protein of Epstein-Barr virus induces cellular phenotypes independently of expression of Bcl-2. *J Virol* 1993; **67**: 5269-5278.
- 195 Peng M, Lundgren E. Transient expression of the Epstein-Barr virus LMP1 gene in human primary B cells induces cellular activation and DNA synthesis. *Oncogene* 1992; **7**: 1775-1782.
- 196 Peng M, Lundgren E. Transient expression of the Epstein-Barr virus LMP1 gene in B-cell chronic lymphocytic leukemia cells, T cells, and hematopoietic cell lines: cell-type-independent-induction of CD23, CD21, and ICAM-1. *Leukemia* 1993; **7**: 104-112.
- 197 Rowe M, Peng-Pilon M, Huen DS, Hardy R, Croom-Carter D, Lundgren E *et al*. Upregulation of bcl-2 by the Epstein-Barr virus latent membrane protein LMP1: a B-cell-specific response that is delayed relative to NF-kappa B activation and to induction of cell surface markers. *J Virol* 1994; **68**: 5602-5612.
- 198 Wang D, Liebowitz D, Wang F, Gregory C, Rickinson A, Larson R *et al*. Epstein-Barr virus latent infection membrane protein alters the human B-lymphocyte phenotype: deletion of the amino terminus abolishes activity. *J Virol* 1988; **62**: 4173-4184.
- 199 Wang F, Gregory C, Sample C, Rowe M, Liebowitz D, Murray R *et al*. Epstein-Barr virus latent membrane protein (LMP1) and nuclear proteins 2 and 3C are effectors of phenotypic changes in B lymphocytes: EBNA-2 and LMP1 cooperatively induce CD23. *J Virol* 1990; **64**: 2309-2318.
- 200 Zhang Q, Brooks L, Busson P, Wang F, Charron D, Kieff E *et al*. Epstein-Barr virus (EBV) latent membrane protein 1 increases HLA class II expression in an EBV-negative B cell line. *Eur J Immunol* 1994; **24**: 1467-1470.
- 201 Yang J, Deng X, Deng L, Gu H, Fan W, Cao Y. Telomerase activation by Epstein-Barr virus latent membrane protein 1 is associated with c-Myc expression in human nasopharyngeal epithelial cells. *J Exp Clin Cancer Res* 2004; **23**: 495-506.
- 202 Liu HP, Chen CC, Wu CC, Huang YC, Liu SC, Liang Y *et al*. Epstein-Barr virus-encoded LMP1 interacts with FGD4 to activate Cdc42 and thereby promote migration of nasopharyngeal carcinoma cells. *PLoS Pathogen* 2012; **8**: e1002690.
- 203 Lo AK, Lo KW, Ko CW, Young LS, Dawson CW. Inhibition of the LKB1-AMPK pathway by the Epstein-Barr virus-encoded LMP1 promotes proliferation and transformation of human nasopharyngeal epithelial cells. *J Pathol* 2013; **230**: 336-346.
- 204 Dutton A, Woodman CB, Chukwuma MB, Last JI, Wei W, Vockerodt M *et al*. Bmi-1 is induced by the Epstein-Barr virus oncogene LMP1 and regulates the expression of viral target genes in Hodgkin lymphoma cells. *Blood* 2007; **109**: 2597-2603.
- 205 Anderton E, Yee J, Smith P, Crook T, White RE, Allday MJ. Two Epstein-Barr virus (EBV) oncoproteins cooperate to repress expression of the proapoptotic tumour-suppressor Bim: clues to the pathogenesis of Burkitt's lymphoma. *Oncogene* 2008; **27**: 421-433.
- 206 Yoshizaki T, Horikawa T, Qing-Chun R, Wakisaka N, Takeshita H, Sheen TS *et al*. Induction of interleukin-8 by Epstein-Barr virus latent membrane protein-1 and its correlation to angiogenesis in nasopharyngeal carcinoma. *Clin Cancer Res* 2001; **7**: 1946-1951.
- 207 Chang MS, Kim DH, Roh JK, Middeldorp JM, Kim YS, Kim S *et al*. Epstein-Barr virus-encoded BARF1 promotes proliferation of gastric carcinoma cells through regulation of NF-kappaB. *J Virol* 2013; **87**: 10515-10523.
- 208 Yasui T, Luftig M, Soni V, Kieff E. Latent infection membrane protein transmembrane FWLY is critical for intermolecular interaction, raft localization, and signaling. *Proc Natl Acad Sci USA* 2004; **101**: 278-283.
- 209 Higuchi M, Izumi KM, Kieff E. Epstein-Barr virus latent-infection membrane proteins are palmitoylated and raft-associated: protein 1 binds to the cytoskeleton through TNF receptor cytoplasmic factors. *Proc Natl Acad Sci USA* 2001; **98**: 4675-4680.
- 210 Hayden MS, Ghosh S. Signaling to NF-kappaB. *Genes Dev* 2004; **18**: 2195-2224.
- 211 Kaye KM, Devergne O, Harada JN, Izumi KM, Yalamanchili R, Kieff E *et al*. Tumor necrosis factor receptor associated factor 2 is a mediator of NF-kappa B activation by latent infection membrane protein 1, the Epstein-Barr virus transforming protein. *Proc Natl Acad Sci USA* 1996; **93**: 11085-11090.
- 212 Ishida T, Mizushima S, Azuma S, Kobayashi N, Tojo T, Suzuki K *et al*. Identification of TRAF6, a novel tumor necrosis factor receptor-associated factor protein that mediates signaling from an amino-terminal domain of the CD40 cytoplasmic region. *J Biol Chem* 1996; **271**: 28745-28748.
- 213 Ansieau S, Scheffrahn I, Mosialos G, Brand H, Duyster J, Kaye K *et al*. Tumor necrosis factor receptor-associated factor (TRAF)-1, TRAF-2, and TRAF-3 interact *in vivo* with the CD30 cytoplasmic domain; TRAF-2 mediates CD30-induced nuclear factor kappa B activation. *Proc Natl Acad Sci USA* 1996; **93**: 14053-14058.
- 214 Eliopoulos AG, Dawson CW, Mosialos G, Floettmann JE, Rowe M, Armitage RJ *et al*. CD40-induced growth inhibition in epithelial cells is mimicked by Epstein-Barr virus-encoded LMP1: involvement of TRAF3 as a common mediator. *Oncogene* 1996; **13**: 2243-2254.
- 215 Devergne O, Cahir McFarland ED, Mosialos G, Izumi KM, Ware CF, Kieff E. Role of the TRAF binding site and NF-kappaB activation in Epstein-Barr virus latent membrane protein 1-induced cell gene expression. *J Virol* 1998; **72**: 7900-7908.
- 216 Devergne O, Hatzivassiliou E, Izumi KM, Kleijnen MF, Kieff E *et al*. Association of TRAF1, TRAF2, and TRAF3 with an Epstein-Barr virus LMP1 domain important for B-lymphocyte transformation: role in NF-kappaB activation. *Mol Cell Biol* 1996; **16**: 7098-7108.
- 217 Sylla BS, Hung SC, Davidson DM, Hatzivassiliou E, Malinin NL, Wallach D *et al*. Epstein-Barr virus-transforming protein latent infection membrane protein 1 activates transcription factor NF-kappaB through a pathway that includes the NF-kappaB-inducing kinase and the IkappaB kinases IKKalpha and IKKbeta. *Proc Natl Acad Sci USA* 1998; **95**: 10106-10111.
- 218 Luftig M, Prinarakis E, Yasui T, Tschritzis T, Cahir-McFarland E, Inoue J *et al*. Epstein-Barr virus latent membrane protein 1 activation of NF-kappaB through IRAK1 and TRAF6. *Proc Natl Acad Sci USA* 2003; **100**: 15595-15600.
- 219 VanArsdale TL, VanArsdale SL, Force WR, Walter BN, Mosialos G, Kieff E *et al*. Lymphotoxin-beta receptor signaling complex: role of tumor necrosis factor receptor-associated factor 3 recruitment in cell death and activation of nuclear factor kappaB. *Proc Natl Acad Sci USA* 1997; **94**: 2460-2465.
- 220 Miller CL, Lee JH, Kieff E, Burkhardt AL, Bolen JB, Longnecker R. Epstein-Barr virus protein LMP2A regulates reactivation from latency by negatively regulating tyrosine kinases involved in slg-mediated signal transduction. *Infect Agents Dis* 1994; **3**: 128-136.
- 221 Mancao C, Hammerschmidt W. Epstein-Barr virus latent membrane protein 2A is a B-cell receptor mimic and essential for B-cell survival. *Blood* 2007; **110**: 3715-3721.
- 222 Ikeda M, Longnecker R. Cholesterol is critical for Epstein-Barr virus latent membrane protein 2A trafficking and protein stability. *Virology* 2007; **360**: 461-468.
- 223 Katzman RB, Longnecker R. LMP2A does not require palmitoylation to localize to buoyant complexes or for function. *J Virol* 2004; **78**: 10878-10887.
- 224 Anderson LJ, Longnecker R. EBV LMP2A provides a surrogate pre-B cell receptor signal through constitutive activation of the ERK/MAPK pathway. *J Gen Virol* 2008; **89**: 1563-1568.
- 225 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 USA* 1994; **91**: 772-776.
- 226 Fukuda M, Kawaguchi Y. Role of the immunoreceptor tyrosine-based activation motif of latent membrane protein 2A (LMP2A) in Epstein-Barr virus LMP2A-induced cell transformation. *J Virol* 2014; **88**: 5189-5194.
- 227 Rochford R, Miller CL, Cannon MJ, Izumi KM, Kieff E, Longnecker R. *In vivo* growth of Epstein-Barr virus transformed B cells with mutations in latent membrane protein 2 (LMP2). *Arch Virol* 1997; **142**: 707-720.

- 228 Speck P, Kline KA, Cheresh P, Longnecker R. Epstein-Barr virus lacking latent membrane protein 2 immortalizes B cells with efficiency indistinguishable from that of wild-type virus. *J Gen Virol* 1999; **80**(Part 8): 2193-2203.
- 229 Incrocci R, McCormack M, Swanson-Mungerson M. Epstein-Barr virus LMP2A increases IL-10 production in mitogen-stimulated primary B-cells and B-cell lymphomas. *J Gen Virol* 2013; **94**: 1127-1133.
- 230 Portis T, Dyck P, Longnecker R. Epstein-Barr virus (EBV) LMP2A induces alterations in gene transcription similar to those observed in Reed-Sternberg cells of Hodgkin lymphoma. *Blood* 2003; **102**: 4166-4178.
- 231 Fish K, Chen J, Longnecker R. Epstein-Barr virus latent membrane protein 2A enhances MYC-driven cell cycle progression in a mouse model of B lymphoma. *Blood* 2014; **123**: 530-540.
- 232 Vrazo AC, Chauchard M, Raab-Traub N, Longnecker R. Epstein-Barr virus LMP2A reduces hyperactivation induced by LMP1 to restore normal B cell phenotype in transgenic mice. *PLoS Pathogen* 2012; **8**: e1002662.
- 233 Swanson-Mungerson M, Bultema R, Longnecker R. Epstein-Barr virus LMP2A imposes sensitivity to apoptosis. *J Gen Virol* 2010; **91**: 2197-2202.
- 234 Biegging KT, Amick AC, Longnecker R. Epstein-Barr virus LMP2A bypasses p53 inactivation in a MYC model of lymphomagenesis. *Proc Natl Acad Sci USA* 2009; **106**: 17945-17950.
- 235 Bultema R, Longnecker R, Swanson-Mungerson M. Epstein-Barr virus LMP2A accelerates MYC-induced lymphomagenesis. *Oncogene* 2009; **28**: 1471-1476.
- 236 Ikeda M, Longnecker R. The c-Cbl proto-oncoprotein downregulates EBV LMP2A signaling. *Virology* 2009; **385**: 183-191.
- 237 Anderson LJ, Longnecker R. Epstein-Barr virus latent membrane protein 2A exploits Notch1 to alter B-cell identity *in vivo*. *Blood* 2009; **113**: 108-116.
- 238 Swanson-Mungerson M, Longnecker R. Epstein-Barr virus latent membrane protein 2A and autoimmunity. *Trends Immunol* 2007; **28**: 213-218.
- 239 Swanson-Mungerson MA, Caldwell RG, Bultema R, Longnecker R. Epstein-Barr virus LMP2A alters *in vivo* and *in vitro* models of B-cell anergy, but not deletion, in response to autoantigen. *J Virol* 2005; **79**: 7355-7362.
- 240 Sutkowski N, Chen G, Calderon G, Huber BT. Epstein-Barr virus latent membrane protein LMP-2A is sufficient for transactivation of the human endogenous retrovirus HERV-K18 superantigen. *J Virol* 2004; **78**: 7852-7860.
- 241 Allen MD, Young LS, Dawson CW. The Epstein-Barr virus-encoded LMP2A and LMP2B proteins promote epithelial cell spreading and motility. *J Virol* 2005; **79**: 1789-1802.
- 242 Chen F, Liu C, Lindvall C, Xu D, Ernberg I. Epstein-Barr virus latent membrane 2A (LMP2A) down-regulates telomerase reverse transcriptase (hTERT) in epithelial cell lines. *Int J Cancer* 2005; **113**: 284-289.
- 243 Iwakiri D, Minamitani T, Samanta M. Epstein-Barr virus latent membrane protein 2A contributes to anoikis resistance through ERK activation. *J Virol* 2013; **87**: 8227-8234.
- 244 Nakaya T, Kikuchi Y, Kunita A, Ishikawa S, Matsusaka K, Hino R *et al*. Enrichment of stem-like cell population comprises transformation ability of Epstein-Barr virus latent membrane protein 2A for non-transformed cells. *Virus Res* 2013; **174**: 108-115.
- 245 Lin Z, Wan X, Jiang R, Deng L, Gao Y, Tang J *et al*. EBV-encoded LMP2A promotes EMT in nasopharyngeal carcinoma via MTA1 and mTOR signaling induction. *J Virol* 2014; **88**: 11872-11885.
- 246 Fotheringham JA, Mazzucca S, Raab-Traub N. Epstein-Barr virus latent membrane protein-2A-induced DeltaNp63alpha expression is associated with impaired epithelial-cell differentiation. *Oncogene* 2010; **29**: 4287-4296.
- 247 Hino R, Uozaki H, Murakami N, Ushiku T, Shinozaki A, Ishikawa S *et al*. Activation of DNA methyltransferase 1 by EBV latent membrane protein 2A leads to promoter hypermethylation of PTEN gene in gastric carcinoma. *Cancer Res* 2009; **69**: 2766-2774.
- 248 Pan YR, Vatsyayan J, Chang YS, Chang HY. Epstein-Barr virus latent membrane protein 2A upregulates UDP-glucose dehydrogenase gene expression via ERK and PI3K/Akt pathway. *Cell Microbiol* 2008; **10**: 2447-2460.
- 249 Shah KM, Stewart SE, Wei W, Woodman CB, O'Neil JD, Dawson CW *et al*. The EBV-encoded latent membrane proteins, LMP2A and LMP2B, limit the actions of interferon by targeting interferon receptors for degradation. *Oncogene* 2009; **28**: 3903-3914.
- 250 Longnecker R, Kieff E. A second Epstein-Barr virus membrane protein (LMP2) is expressed in latent infection and colocalizes with LMP1. *J Virol* 1990; **64**: 2319-2326.
- 251 Tomaszewski-Flick MJ, Rowe DT. Minimal protein domain requirements for the intracellular localization and self-aggregation of Epstein-Barr virus latent membrane protein 2. *Virus Genes* 2007; **35**: 225-234.
- 252 Rovedo M, Longnecker R. Epstein-Barr virus latent membrane protein 2A preferentially signals through the Src family kinase Lyn. *J Virol* 2008; **82**: 8520-8528.
- 253 Longnecker R, Druker B, Roberts TM, Kieff E. An Epstein-Barr virus protein associated with cell growth transformation interacts with a tyrosine kinase. *J Virol* 1991; **65**: 3681-3692.
- 254 Scholle F, Longnecker R, Raab-Traub N. Epithelial cell adhesion to extracellular matrix proteins induces tyrosine phosphorylation of the Epstein-Barr virus latent membrane protein 2: a role for C-terminal Src kinase. *J Virol* 1999; **73**: 4767-4775.
- 255 Rechsteiner MP, Berger C, Zauner L, Sigrist JA, Weber M, Longnecker R *et al*. Latent membrane protein 2B regulates susceptibility to induction of lytic Epstein-Barr virus infection. *J Virol* 2008; **82**: 1739-1747.
- 256 Rovedo M, Longnecker R. Epstein-Barr virus latent membrane protein 2B (LMP2B) modulates LMP2A activity. *J Virol* 2007; **81**: 84-94.
- 257 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**: 3068-3074.
- 258 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**: 232-242.
- 259 Chen A, Divisconte M, Jiang X, Quink C, Wang F. Epstein-Barr virus with the latent infection nuclear antigen 3B completely deleted is still competent for B-cell growth transformation *in vitro*. *J Virol* 2005; **79**: 4506-4509.
- 260 Maruo S, Johannsen E, Illanes D, Cooper A, Kieff E. Epstein-Barr virus nuclear protein EBNA3A is critical for maintaining lymphoblastoid cell line growth. *J Virol* 2003; **77**: 10437-10447.
- 261 Maruo S, Wu Y, Ishikawa S, Kanda T, Iwakiri D, Takada K. Epstein-Barr virus nuclear protein EBNA3C is required for cell cycle progression and growth maintenance of lymphoblastoid cells. *Proc Natl Acad Sci USA* 2006; **103**: 19500-19505.
- 262 Cooper A, Johannsen E, Maruo S, Cahir-McFarland E, Illanes D, Davidson D *et al*. EBNA3A association with RBP-Jkappa down-regulates c-myc and Epstein-Barr virus-transformed lymphoblast growth. *J Virol* 2003; **77**: 999-1010.
- 263 Zhao B, Marshall DR, Sample CE. A conserved domain of the Epstein-Barr virus nuclear antigens 3A and 3C binds to a discrete domain of Jkappa. *J Virol* 1996; **70**: 4228-4236.
- 264 Banerjee S, Lu J, Cai Q, Saha A, Jha HC, Dzung RK *et al*. The EBV latent antigen 3C inhibits apoptosis through targeted regulation of interferon regulatory factors 4 and 8. *PLoS Pathogen* 2013; **9**: e1003314.
- 265 Zhao B, Sample CE. Epstein-Barr virus nuclear antigen 3C activates the latent membrane protein 1 promoter in the presence of Epstein-Barr virus nuclear antigen 2 through sequences encompassing an spi-1/Spi-B binding site. *J Virol* 2000; **74**: 5151-5160.
- 266 Harth-Hertle ML, Scholz BA, Erhard F, Glaser LV, Dolken L, Zimmer R *et al*. Inactivation of intergenic enhancers by EBNA3A initiates and maintains polycomb signatures across a chromatin domain encoding CXCL10 and CXCL9. *PLoS Pathogen* 2013; **9**: e1003638.
- 267 Paschos K, Smith P, Anderton E, Middeldorp JM, White RE, Allday MJ. Epstein-Barr virus latency in B cells leads to epigenetic repression and CpG methylation of the tumour suppressor gene Bim. *PLoS Pathogen* 2009; **5**: e1000492.
- 268 Bazot Q, Deschamps T, Tafforeau L, Siouda M, Leblanc P, Harth-Hertle ML *et al*. Epstein-Barr virus nuclear antigen 3A protein regulates CDKN2B transcription via interaction with MIZ-1. *Nucleic Acids Res* 2014; **42**: 9700-9716.
- 269 Maruo S, Wu Y, Ito T, Kanda T, Kieff ED, Takada K. Epstein-Barr virus nuclear protein EBNA3C residues critical for maintaining lymphoblastoid cell growth. *Proc Natl Acad Sci USA* 2009; **106**: 4419-4424.
- 270 Maruo S, Zhao B, Johannsen E, Kieff E, Zou J, Takada K. Epstein-Barr virus nuclear antigens 3C and 3A maintain lymphoblastoid cell growth by repressing p16INK4A and p14ARF expression. *Proc Natl Acad Sci USA* 2011; **108**: 1919-1924.

- 271 Hertle ML, Popp C, Petermann S, Maier S, Kremmer E, Lang R *et al*. Differential gene expression patterns of EBV infected EBNA-3A positive and negative human B lymphocytes. *PLoS Pathogen* 2009; **5**: e1000506.
- 272 Skalska L, White RE, Parker GA, Turro E, Sinclair AJ, Paschos K *et al*. Induction of p16(INK4a) is the major barrier to proliferation when Epstein-Barr virus (EBV) transforms primary B cells into lymphoblastoid cell lines. *PLoS Pathogen* 2013; **9**: e1003187.
- 273 Lee S, Sakakibara S, Maruo S, Zhao B, Calderwood MA, Holthaus AM *et al*. Epstein-Barr virus nuclear protein 3C domains necessary for lymphoblastoid cell growth: interaction with RBP-Jkappa regulates TCL1. *J Virol* 2009; **83**: 12368–12377.
- 274 White RE, Ramer PC, Naresh KN, Meixlsperger S, Pinaud L, Rooney C *et al*. EBNA3B-deficient EBV promotes B cell lymphomagenesis in humanized mice and is found in human tumors. *J Clin Invest* 2012; **122**: 1487–1502.
- 275 Allday MJ, Farrell PJ. Epstein-Barr virus nuclear antigen EBNA3C/6 expression maintains the level of latent membrane protein 1 in G1-arrested cells. *J Virol* 1994; **68**: 3491–3498.
- 276 Zhao B, Mar JC, Maruo S, Lee S, Gewurz BE, Johannsen E *et al*. Epstein-Barr virus nuclear antigen 3C regulated genes in lymphoblastoid cell lines. *Proc Natl Acad Sci USA* 2011; **108**: 337–342.
- 277 Saha A, Robertson ES. Functional modulation of the metastatic suppressor Nm23-H1 by oncogenic viruses. *FEBS Lett* 2011; **585**: 3174–3184.
- 278 Knight JS, Lan K, Subramanian C, Robertson ES. Epstein-Barr virus nuclear antigen 3C recruits histone deacetylase activity and associates with the corepressors mSin3A and NCoR in human B-cell lines. *J Virol* 2003; **77**: 4261–4272.
- 279 Saha A, Halder S, Upadhyay SK, Lu J, Kumar P, Murakami M *et al*. Epstein-Barr virus nuclear antigen 3C facilitates G1-S transition by stabilizing and enhancing the function of cyclin D1. *PLoS Pathogen* 2011; **7**: e1001275.
- 280 Saha A, Bamidele A, Murakami M, Robertson ES. EBNA3C attenuates the function of p53 through interaction with inhibitor of growth family proteins 4 and 5. *J Virol* 2011; **85**: 2079–2088.
- 281 Jha HC, A J MP, Saha A, Banerjee S, Lu J, Robertson ES. Epstein-Barr virus essential antigen EBNA3C attenuates H2AX expression. *J Virol* 2014; **88**: 3776–3788.
- 282 Banerjee S, Lu J, Cai Q, Sun Z, Jha HC, Robertson ES. EBNA3C augments Pim-1 mediated phosphorylation and degradation of p21 to promote B-cell proliferation. *PLoS Pathogen* 2014; **10**: e1004304.
- 283 Jha HC, Lu J, Saha A, Cai Q, Banerjee S, Prasad MA *et al*. EBNA3C-mediated regulation of aurora kinase B contributes to Epstein-Barr virus-induced B-cell proliferation through modulation of the activities of the retinoblastoma protein and apoptotic caspases. *J Virol* 2013; **87**: 12121–12138.
- 284 Saha A, Murakami M, Kumar P, Bajaj B, Sims K, Robertson ES. Epstein-Barr virus nuclear antigen 3C augments Mdm2-mediated p53 ubiquitination and degradation by deubiquitinating Mdm2. *J Virol* 2009; **83**: 4652–4669.
- 285 Yi F, Saha A, Murakami M, Kumar P, Knight JS, Cai Q *et al*. Epstein-Barr virus nuclear antigen 3C targets p53 and modulates its transcriptional and apoptotic activities. *Virology* 2009; **388**: 236–247.
- 286 Knight JS, Sharma N, Robertson ES. Epstein-Barr virus latent antigen 3C can mediate the degradation of the retinoblastoma protein through an SCF cellular ubiquitin ligase. *Proc Natl Acad Sci USA* 2005; **102**: 18562–18566.
- 287 Saha A, Lu J, Morizur L, Upadhyay SK, Aj MP, Robertson ES. E2F1 mediated apoptosis induced by the DNA damage response is blocked by EBV nuclear antigen 3C in lymphoblastoid cells. *PLoS Pathogen* 2012; **8**: e1002573.
- 288 Piovon E, Tosello V, Indraccolo S, Cabrelle A, Baesso I, Trentin L *et al*. Chemokine receptor expression in EBV-associated lymphoproliferation in hu/SCID mice: implications for CXCL12/CXCR4 axis in lymphoma generation. *Blood* 2005; **105**: 931–939.
- 289 Skalska L, White RE, Franz M, Ruhmann M, Allday MJ. Epigenetic repression of p16(INK4A) by latent Epstein-Barr virus requires the interaction of EBNA3A and EBNA3C with CtBP. *PLoS Pathogen* 2010; **6**: e1000951.
- 290 McClellan MJ, Wood CD, Ojeniyi O, Cooper TJ, Kanhere A, Arvey A *et al*. Modulation of enhancer looping and differential gene targeting by Epstein-Barr virus transcription factors directs cellular reprogramming. *PLoS Pathogen* 2013; **9**: e1003636.
- 291 Jiang S, Willox B, Zhou H, Holthaus AM, Wang A, Shi TT *et al*. Epstein-Barr virus nuclear antigen 3C binds to BATF/IRF4 or SPI1/IRF4 composite sites and recruits Sin3A to repress CDKN2A. *Proc Natl Acad Sci USA* 2014; **111**: 421–426.
- 292 Paschos K, Parker GA, Watanatanasup E, White RE, Allday MJ. BIM promoter directly targeted by EBNA3C in polycomb-mediated repression by EBV. *Nucleic Acids Res* 2012; **40**: 7233–7246.
- 293 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 USA* 1981; **78**: 805–809.
- 294 Rymo L. Identification of transcribed regions of Epstein-Barr virus DNA in Burkitt lymphoma-derived cells. *J Virol* 1979; **32**: 8–18.
- 295 Iwakiri D. Epstein-Barr virus-encoded RNAs: key molecules in viral pathogenesis. *Cancers (Basel)* 2014; **6**: 1615–1630.
- 296 Rosa MD, Gottlieb E, Lerner MR, Steitz JA. Striking similarities are exhibited by two small Epstein-Barr virus-encoded ribonucleic acids and the adenovirus-associated ribonucleic acids VA1 and VAII. *Mol Cell Biol* 1981; **1**: 785–796.
- 297 Gregorovic G, Bosshard R, Karstegl CE, White RE, Pattle S, Chiang AK *et al*. Cellular gene expression that correlates with EBER expression in Epstein-Barr Virus-infected lymphoblastoid cell lines. *J Virol* 2011; **85**: 3535–3545.
- 298 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**: 4298–4307.
- 299 Komano J, Maruo S, Kurozumi K, Oda T, Takada K. Oncogenic role of Epstein-Barr virus-encoded RNAs in Burkitt's lymphoma cell line Akata. *J Virol* 1999; **73**: 9827–9831.
- 300 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**: 9844–9853.
- 301 Repellin CE, Tsimbouri PM, Philbey AW, Wilson JB. Lymphoid hyperplasia and lymphoma in transgenic mice expressing the small non-coding RNA, EBER1 of Epstein-Barr virus. *PLoS One* 2010; **5**: e9092.
- 302 Nanbo A, Takada K. The role of Epstein-Barr virus-encoded small RNAs (EBERs) in oncogenesis. *Rev Med Virol* 2002; **12**: 321–326.
- 303 Kitagawa N, Goto M, Kurozumi K, Maruo S, Fukayama M, Naoe T *et al*. Epstein-Barr virus-encoded poly(A)(-) RNA supports Burkitt's lymphoma growth through interleukin-10 induction. *EMBO J* 2000; **19**: 6742–6750.
- 304 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**: 7062–7067.
- 305 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**: 1767–1773.
- 306 Yang L, Aozasa K, Oshimi K, Takada K. Epstein-Barr virus (EBV)-encoded RNA promotes growth of EBV-infected T cells through interleukin-9 induction. *Cancer Res* 2004; **64**: 5332–5337.
- 307 Samanta M, Iwakiri D, Kanda T, Imaizumi T, Takada K. EB virus-encoded RNAs are recognized by RIG-I and activate signaling to induce type I IFN. *EMBO J* 2006; **25**: 4207–4214.
- 308 Iwakiri D, Zhou L, Samanta M, Matsumoto M, Ebihara T, Seya T *et al*. Epstein-Barr virus (EBV)-encoded small RNA is released from EBV-infected cells and activates signaling from Toll-like receptor 3. *J Exp Med* 2009; **206**: 2091–2099.
- 309 Toczyski DP, Steitz JA. The cellular RNA-binding protein EAP recognizes a conserved stem-loop in the Epstein-Barr virus small RNA EBER 1. *Mol Cell Biol* 1993; **13**: 703–710.
- 310 Lee N, Pimienta G, Steitz JA. AUF1/hnRNP D is a novel protein partner of the EBER1 noncoding RNA of Epstein-Barr virus. *RNA* 2012; **18**: 2073–2082.
- 311 Clarke PA, Sharp NA, Clemens MJ. Translational control by the Epstein-Barr virus small RNA EBER-1. Reversal of the double-stranded RNA-induced inhibition of protein synthesis in reticulocyte lysates. *Eur J Biochem* 1990; **193**: 635–641.
- 312 McKenna SA, Lindhout DA, Shimoike T, Aitken CE, Puglisi JD. Viral dsRNA inhibitors prevent self-association and autophosphorylation of PKR. *J Mol Biol* 2007; **372**: 103–113.
- 313 Katze MG, Wambach M, Wong ML, Garfinkel M, Meurs E, Chong K *et al*. Functional expression and RNA binding analysis of the interferon-induced, double-stranded RNA-activated, 68,000-Mr protein kinase in a cell-free system. *Mol Cell Biol* 1991; **11**: 5497–5505.

- 314 Sharp TV, Schwemmler M, Jeffrey I, Laing K, Mellor H, Proud CG *et al.* Comparative analysis of the regulation of the interferon-inducible protein kinase PKR by Epstein–Barr virus RNAs EBER-1 and EBER-2 and adenovirus VAI RNA. *Nucleic Acids Res* 1993; **21**: 4483–4490.
- 315 Fok V, Mitton-Fry RM, Grech A, Steitz JA. Multiple domains of EBER 1, an Epstein–Barr virus noncoding RNA, recruit human ribosomal protein L22. *RNA* 2006; **12**: 872–882.
- 316 Elia A, Vyas J, Laing KG, Clemens MJ. Ribosomal protein L22 inhibits regulation of cellular activities by the Epstein–Barr virus small RNA EBER-1. *Eur J Biochem* 2004; **271**: 1895–1905.
- 317 Kang DC, Gopalkrishnan RV, Wu Q, Jankowsky E, Pyle AM, Fisher PB. Mda-5: An interferon-inducible putative RNA helicase with double-stranded RNA-dependent ATPase activity and melanoma growth-suppressive properties. *Proc Natl Acad Sci USA* 2002; **99**: 637–642.
- 318 Cai X, Schafer A, Lu S, Bilello JP, Desrosiers RC, Edwards R *et al.* Epstein–Barr virus microRNAs are evolutionarily conserved and differentially expressed. *PLoS Pathogen* 2006; **2**: e23.
- 319 Pratt ZL, Kuzembayeva M, Sengupta S, Sugden B. The microRNAs of Epstein–Barr Virus are expressed at dramatically differing levels among cell lines. *Virology* 2009; **386**: 387–397.
- 320 Imig J, Motsch N, Zhu JY, Barth S, Okoniewski M, Reineke T *et al.* microRNA profiling in Epstein–Barr virus-associated B-cell lymphoma. *Nucleic Acids Res* 2011; **39**: 1880–1893.
- 321 Marquitz AR, Mathur A, Chugh PE, Dittmer DP, Raab-Traub N. Expression profile of microRNAs in Epstein–Barr virus-infected AGS gastric carcinoma cells. *J Virol* 2014; **88**: 1389–1393.
- 322 Kuzembayeva M, Hayes M, Sugden B. Multiple functions are mediated by the miRNAs of Epstein–Barr virus. *Curr Opin Virol* 2014; **7C**: 61–65.
- 323 Xia T, O'Hara A, Araujo I, Barreto J, Carvalho E, Sapucaia JB *et al.* EBV microRNAs in primary lymphomas and targeting of CXCL-11 by ebv-mir-BHRF1-3. *Cancer Res* 2008; **68**: 1436–1442.
- 324 Nachmani D, Stern-Ginossar N, Sarid R, Mandelboim O. Diverse herpesvirus microRNAs target the stress-induced immune ligand MICB to escape recognition by natural killer cells. *Cell Host Microbe* 2009; **5**: 376–385.
- 325 Haneklaus M, Gerlic M, Kurowska-Stolarska M, Rainey AA, Pich D, McInnes IB *et al.* Cutting edge: miR-223 and EBV miR-BART15 regulate the NLRP3 inflammasome and IL-1 β production. *J Immunol* 2012; **189**: 3795–3799.
- 326 Feederle R, Haar J, Bernhardt K, Linnstaedt SD, Bannert H, Lips H *et al.* The members of an Epstein–Barr virus microRNA cluster cooperate to transform B lymphocytes. *J Virol* 2011; **85**: 9801–9810.
- 327 Seto E, Moosmann A, Gromminger 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 Pathogen* 2010; **6**: e1001063.
- 328 Wahl A, Linnstaedt SD, Esoda C, Krisko JF, Martinez-Torres F, Delecluse HJ *et al.* A cluster of virus-encoded microRNAs accelerates acute systemic Epstein–Barr virus infection but does not significantly enhance virus-induced oncogenesis *in vivo*. *J Virol* 2013; **87**: 5437–5446.
- 329 Vereide DT, Seto E, Chiu YF, Hayes M, Tagawa T, Grundhoff A *et al.* Epstein–Barr virus maintains lymphomas via its miRNAs. *Oncogene* 2014; **33**: 1258–1264.
- 330 Choi H, Lee H, Kim SR, Gho YS, Lee SK. Epstein–Barr virus-encoded microRNA BART15-3p promotes cell apoptosis partially by targeting BRUCE. *J Virol* 2013; **87**: 8135–8144.
- 331 Nikitin PA, Yan CM, Forte E, Bocedi A, Tourigny JP, White RE *et al.* An ATM/Chk2-mediated DNA damage-responsive signaling pathway suppresses Epstein–Barr virus transformation of primary human B cells. *Cell Host Microbe* 2010; **8**: 510–522.
- 332 Kim SY, Song KA, Kieff E, Kang MS. Small molecule and peptide-mediated inhibition of Epstein–Barr virus nuclear antigen 1 dimerization. *Biochem Biophys Res Commun* 2012; **424**: 251–256.
- 333 Lee EK, Kim SY, Noh KW, Joo EH, Zhao B, Kieff E *et al.* Small molecule inhibition of Epstein–Barr virus nuclear antigen-1 DNA binding activity interferes with replication and persistence of the viral genome. *Antiviral Res* 2014; **104**: 73–83.
- 334 Kang MS, Lee EK, Soni V, Lewis TA, Koehler AN, Srinivasan V *et al.* Roscovitine inhibits EBNA1 serine 393 phosphorylation, nuclear localization, transcription, and episome maintenance. *J Virol* 2011; **85**: 2859–2868.
- 335 Thompson S, Messick T, Schultz DC, Reichman M, Lieberman PM. Development of a high-throughput screen for inhibitors of Epstein–Barr virus EBNA1. *J Biomol Screen* 2010; **15**: 1107–1115.
- 336 Li N, Thompson S, Schultz DC, Zhu W, Jiang H, Luo C *et al.* Discovery of selective inhibitors against EBNA1 via high throughput *in silico* virtual screening. *PLoS One* 2010; **5**: e10126.



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