Published in final edited form as:

Curr Opin Hematol. 2014 July ; 21(4): 358–368. doi:10.1097/MOH.0000000000000060.

How do viruses trick B-cells into becoming lymphomas?

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Abstract

Purpose of review—Since the discovery of EBV in Burkitt lymphoma 50 years ago, only one other virus, namely KSHV/HHV-8, has been confirmed to be a direct cause of B cell lymphoma. Here we will review the evidence for EBV and KSHV as causal lymphoma agents.

Recent findings—A deeper understanding of specific mechanisms by which EBV and KSHV cause B cell lymphomas has been acquired over the past years, in particular with respect to viral protein interactions with host cell pathways, microRNA functions. Specific therapies based on knowledge of viral functions are beginning to be evaluated, mostly in pre-clinical models.

Summary—Understanding the causal associations of specific infections agents with certain B cell lymphomas has allowed more accurate diagnosis and classification. A deeper knowledge of the specific mechanisms of transformation is essential to begin assessing whether virus-targeted treatment modalities may be used in the future.

Keywords

Lymphoma; Epstein Barr virus (EBV); Kaposi's sarcoma herpesvirus (KSHV/HHV-8); Human immunodeficiency virus (HIV); AIDS

Introduction

Two viruses have been firmly linked to B-cell lymphoma pathogenesis in humans: EBV (now formally designated as HHV-4), and KSHV (HHV-8). Both of these are gamma-herpesviruses that can establish a latent infection where infectious virions are not produced, but proteins and non-coding RNAs expressed can affect the cell cycle, promote cellular proliferation, and inhibit apoptosis. These effects are believed to be necessary for these viruses to survive in the appropriate host cellular reservoir as part of their natural life cycle. While expression of viral proteins is usually kept in check by a normal immune response, they also provide the driving force for lymphoma formation in individuals with immunodeficiency, as well as in immunocompetent individuals, albeit more rarely.

The incidence of cancer is greatly increased in HIV-infected individuals, with an approximate 15-fold increase for B cell non-Hodgkin's lymphoma (NHL), which has led the

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There are no conflicts of interest.

Disclosure: Dr. Cesarman is funded by the National Institutes of Health.

WHO to classify HIV-1 as an infectious carcinogen (1, 2). EBV is present in approximately 30% and KSHV in 5% of all AIDS related lymphomas (ARLs) (3), implying that the majority of ARLs have an etiology not yet ascribed to any known virus other than HIV. Since HIV itself is not found in the lymphoma cells in patients with ARL, it has been proposed it acts indirectly by eliciting immunosuppression. However, some enigmas remain. For example, patients with congenital or iatrogenic immune deficiencies also have increased incidence of B cell lymphoma, but the vast majority of these are associated with EBV infection. This raises the question of what are the oncogenic events in the majority of ARLs, which are negative for EBV and KSHV? Here we will review the latest evidence exploring how EBV, KSHV and HIV might induce B cell neoplasia.

Text of review

In this section we will review the specific known mechanism used by EBV and KSHV in the transformation of B cells, with emphasis of proteins and miRNAs with known relevant functions and recent progress in their understanding.

EBV-mediated lymphomagenesis

During long term infection in humans EBV establishes latency in memory B cells, but lytic reactivation leading to production of viral particles occurs upon activation of the B cell receptor (BCR) and plasma cell differentiation (reviewed in (4)). Latency is promoted in B cells by expression of PAX5, which blocks the function of the EBV protein ZEBRA (also called Z or ZTA), that is essential for expression of lytic viral genes (5)**. Most studies indicate that infected lymphoma cells express only a limited number of viral proteins in one of three canonical latency patterns (6). While in actuality the pattern of EBV gene expression can be quite heterogeneous, this simplified classification can help understand the relationship between EBV infection and B cell lymphoma development. The major proteins and RNAs expressed and their functions are described in Table 1, where recently discovered functions are referenced (7–9). In Latency I, EBNA-1 protein and EBERs are expressed. On the other end of the spectrum, Latency III involves the unrestricted expression of all 9 latent genes including six EBV-encoded nuclear antigens (EBNA-1, -2, 3A–C and LP), and three latent membrane proteins (LMP-1, LMP-2A, and LMP-2B). These viral proteins are highly immunogenic, so latency III occurs in severely immunodeficient individuals and in lymphoblastoid cell lines, which are B-cells immortalized by EBV infection *in vitro*. Latency II is an intermediate pattern with expression of EBNA1 plus LMP1 and LMP2 (10).

EBV also expresses non-coding RNAs, including EBERs, which are expressed ubiquitously and abundantly in infected cells, having become a useful diagnostic technique for EBV infection using *in situ* hybridization. Viral microRNAs (miRs) are also expressed in latently-infected tumor cells. At least 22 precursors and 44 mature EBV miRs have been described (11, 12). There is some variation of which miRs are expressed depending on cell type and experimental context. A cluster of miRs, called BHRF1 miRs, is expressed in latency III B cells and at low levels in cells with latency I (13, 14). miRs in the *BHRF1* region inhibit apoptosis and favor cell cycle progression and proliferation during the early phase of infected human primary B cells (15).

From the epigenetic standpoint, EBV infection of B cells results in the appearance of large-scale hypomethylated blocks in about two-thirds of the genome, and these regions overlap with hypomethylated blocks seen in general in cancer and are associated with gene expression hypervariability (16)**.

Mechanisms of KSHV-mediated lymphomagenesis

KSHV encodes a remarkable number of proteins with cellular homologues and potential roles in oncogenesis, but many of these are expressed during lytic replication, and thus not in a majority of tumor cells. For example, one lytic gene is the viral BCL2 homolog, that may be important to keep the infected cells alive long enough to complete the viral life cycle. However, lymphoma cells are largely latent, and only a handful of viral proteins are made, which are important for viral episome maintenance, cell proliferation, cell survival and immune evasion. Three viral gene products are clearly abundantly expressed in all latently infected cells: LANA, vCYC and vFLIP. Other viral gene products are expressed in a subset of cells in lymphoma or multicentric Castleman disease (MCD), which are Kaposin B, vIL-6, and vIRF3. The main feature of these proteins and their role in oncogenesis is summarized in Table 2, where recently described functions for LANA (17–20), vFLIP (21), vIL6 (22, 23), vIRF3 (24) and Kaposin B (25), are underlined.

KSHV encodes at least 12 pre-miRNAs, which cluster in the K12/Kaposin genomic locus and are expressed in latently infected cells (26–30). A recent study showed that deletion of a cluster of 10 precursor miRs from the KSHV genome rendered it unable to transform in vitro infected cells, and rather caused cell cycle arrest and apoptosis, revealing that in the context of whole virus infection, these miRs play a protective role on the infected cell (31). Studies assessing specific miR functions include the finding that miR-K1 can target I κ B α , an inhibitor of NF- κ B, thereby strengthening the NF- κ B activity induced by vFLIP and promoting cellular survival (32). miR-K1 also targets cellular mRNAs encoding cyclin-dependent kinase inhibitor CDKN1a (p21), thus blocking cell cycle arrest and promoting cellular proliferation (33). miR-K12-11 is a viral ortholog of cellular miR-155, and both the viral and cellular counterparts have been shown to promote B cell expansion (34–36). Deep sequencing has shown that both cellular and viral microRNA are present in virions, suggesting that they can be functional immediately after de novo infection (37). Unbiased global analysis of microRNA function, specifically PAR-CLIP and Ago HITS-CLIP, revealed that KSHV microRNAs target 1000–2000 cellular mRNAs in PEL cell lines. These are enriched for genes involved in many pathways relevant to KSHV pathogenesis, including apoptosis, cell cycle regulation, lymphocyte proliferation, and immune evasion (38, 39).

Virus Associated B Cell Lymphomas

In this section we will provide an updated overview of the major specific B cell lymphoma subtypes that are associated with viral infection (40) (illustrated in Figure 1).

Diffuse large B cell lymphomas (DLBCL)—These lymphomas occur in both HIV-infected and uninfected individuals, but there are some differences among these groups. EBV infection is more common in AIDS-related DLBCL, and some of the EBV+ DLBCLs

have an immunoblastic morphology, including the majority of those presenting as primary in the CNS. In this immunoblastic type, EBV most commonly has a type III latency, and occurs in people with more advanced immunodeficiency because the viral proteins expressed, including LMP1 and EBNA2, are oncogenic but also immunogenic (reviewed in (40)). The frequency of immunoblastic cases has decreased with the use of combined antiretroviral therapy (CART). In contrast, cases with centroblastic morphology occur in patients with or without AIDS, and in HIV-infected patients EBV is present in approximately 30% and most commonly has a type I latency (41–43). In HIV infected patients there was increased proliferation with approximately half of the cases expressing Ki67 in more than 80% of the tumor cells as compared to 13% in HIV-negative patients, indicating that these are more frequently high grade (44). In addition AIDS-DLBCLs had more common *MYC* rearrangements, reduced CD4+ and FOXP3+ T cells, as well as increased activated cytotoxic cells and higher blood vessel density. The presence of EBV in AIDS-related DLBCL has been reported to be associated with a worse clinical outcome (45, 46), but this was not found in a different cohort (41).

Burkitt lymphomas (BL)—While the majority of endemic BL is associated with EBV infection, only approximately a third of cases of sporadic or AIDS related cases will be EBV-positive. A recent study showed that sporadic BL in the United States is associated with EBV in 29% of the cases, but that infection varies with age, being more common in young adults than in children or older individuals, as well as with race (being more common in Blacks and Hispanics), and with HIV status (64% in HIV+ vs. 22% in HIV–) (47).

While BL typically displays EBV type I latency, a different latency pattern, called Wp-restricted latency, was also reported to occur in approximately 15% of Burkitt lymphoma (BL) specimens that have a mutant EBV genome with deletions that include EBNA2 leading to expression of EBNA 3A, 3B, 3C proteins, in addition to EBNA1, in the absence of EBNA2 and the LMPs (48). BL cells that have this deleted version of EBV were reported to have a higher resistance to apoptosis, due to expression of a viral BCL2 homologue, called BHRF1, normally a lytic gene but expressed in latently infected cells by this EBV variant (49). This is important in the context of deregulated *MYC* expression, which is a molecular hallmark of BL (50–54). *MYC* protein overexpression would lead to apoptosis without protective mechanisms such as deletion of TP53 (another common molecular alteration in BL), or in this case, BHRF1 (EBV BCL2) expression.

Classical Hodgkin lymphoma (cHL)—This disease occurs in both HIV infected and uninfected individuals, but there is a more common association with EBV in the former. In addition, while the nodular sclerosis subtype is more common in the general population, the mixed cellularity or lymphocyte depleted forms of CHL comprise most cases in HIV+ patients (55, 56), consistent with the generally increased frequency of EBV infection in the mixed cellularity histological subtype. The number of tumor-associated macrophages (an adverse prognostic factor), is higher in both the mixed cellularity subtype and in EBV-positive cases of cHL(57). Associations with specific HLA types has been reported in cHL, where an increase of HLA-DR2 and HLA-DR5 were found to be increased in EBV-negative cHL, while the allele frequencies of HLA-A1, HLA-B37 and HLA-DR10 were significantly

increased in the EBV-positive cHL population indicating specific genetic predispositions for different subtypes (58).

The EBV proteins expressed in cHL include LMP-1 and LMP-2A. LMP-1 is able to constitutively activate NF- κ B, a pathway known to be activated in cHL (whether associated with EBV or not). Loss of function mutations of TNFAIP3 (A20), an inhibitor of NF- κ B frequently altered in CHL, are less common in EBV+ lymphomas where LMP1 is expressed (59), an observation also made in other EBV+ lymphomas types (60). LMP-1 was recently reported to upregulate discoidin domain receptor 1 (DDR1), a receptor tyrosine kinase that acts as a pro-survival factor and is activated by collagen (61). Thus, collagen in EBV+ cHL nodes may promote the survival of Hodgkin Reed-Sternberg (HRS) cells, and may be one of the reasons why these cells do not survive in cell culture.

BCR is not expressed in cHL, despite the B cell origin of the HRS cells. It is thought that in the EBV-positive cases, LMP-2A replaces BCR by signaling through an ITAM motif and activating the same downstream pathways. However, BCR activation of EBV infected cells leads to EBV lytic reactivation, raising the question of how LMP2A can signal while maintaining latency. This may be explained by recent study that showed that HRS cells do not express a set of genes that are induced by LMP-2A and BCR activation in other cell types, among which EGR1, which is a zinc-finger protein required for BCR-induced EBV replication (62). Thus, even in the presence of LMP-2A expression (and BCR-like signaling), EBV can remain latent in HRS cells.

Post-transplant lymphoproliferative disorders (PTLD)—EBV is present in the majority of PTLDs and, consistent with the immunodeficient state of the host, most lesions harbor an EBV Latency III. The exception are the monomorphic cases which may be EBV negative or have a latency pattern that corresponds to the lymphoma subtype, such as Latency I in DLBCL. A recent gene expression profiling of post-transplant DLBCL revealed a viral and inflammatory response signatures that segregated with the EBV+ cases and latency subtypes, confirming that there are biological differences among these subtypes that may impact on clinical behavior and response to specific therapies (63).

Plasmablastic lymphoma (PBL)—This aggressive malignancy was first reported in the oral cavity of HIV-infected individuals (64), but can also occur in other sites, as well as in immunocompetent individuals (65). The vast majority of cases in the oral cavity are EBV-infected, but in other sites EBV can be found in around 75% of cases. A recent report of five cases with a review of the literature identified 248 PBL cases, out of which 157 were in HIV-positive patients, 43% were outside the oral cavity and EBV was identified in 86% (66). This disease is associated with a restricted type I EBV latency.

Primary effusion lymphoma (PEL)—The presence of KSHV is a defining feature of this disease, although over 90% of cases are doubly infected by EBV (56, 67, 68). Several KSHV proteins are expressed, but EBV has a type I latency, with little or no expression of the major EBV transforming proteins (69, 70). EBV microRNAs are also expressed in PEL (38, 71), providing EBV contributory functions to PEL pathogenesis. For example, KSHV miRNAs directly target more than 2000 cellular mRNAs in PEL cells, including those

involved in transcriptional regulation and signaling, and . 58% of these mRNAs are also targeted by EBV miRNAs, via distinct binding sites (38).

In addition to classical PEL, KSHV can be found in the tumor cells of some rare cases of AIDS-related NHL with no evidence of body cavity involvement. These have been called solid or extracavitary PEL and represent approximately 5% of all AIDS-NHLs. They typically have the morphology of immunoblastic lymphoma but like PELs, they frequently lack of expression of B cell antigens and are also commonly co-infected with EBV (72).

Cases of primary lymphomatous effusions that lack KSHV have been reported, which have been called KSHV- or HHV-8-negative PEL. These occur in HIV-negative and older individuals than KSHV-associated PEL, representing a different disease entity (73–78).

Interesting virus-host cell interactions with implications for transformation and therapy have been recently documented. For example, the viral protein vFLIP is essential for the survival of PEL cells, and it was found to be in complex with IKK γ (NEMO) and HSP90, forming a signalosome that induces NF- κ B. Thus, HSP90 inhibitors have been used to destabilize this signaling complex (79, 80). A proteomic analysis of proteins binding to Hsp90 in PEL cells yielded many proteins involved in the intrinsic apoptosis pathway as HSP90 clients. Accordingly treatment of PEL cells with inhibitor of anti-apoptotic proteins (Obatoclax) synergized with HSP90 inhibition (79). In some experimental systems, HSP90 inhibition can also reduce levels of LANA, another latent gene with oncogenic potential, possibly contributing to cellular toxicity (81). Another recent study showed that neomycin and neamine can reduce tumor growth in mice with a xenograft model of PEL through a mechanism that involved suppression of angiogenin (ANG), which in turn results in reduced KSHV latent gene expression and increased lytic gene expression (82). Directly inducing lytic gene expression has also been used to induce cell death in KSHV-infected PEL cells. This has been achieved using a combination of bortezomib and the histone deacetylase (HDAC) inhibitor suberoylanilidehydroxamic acid (SAHA, also known as vorinostat), which led to prolonged survival in a mouse model of PEL, with elimination of PEL cells, surprisingly without increased viremia (83). Sphingosine kinase (SPHK)-inhibitor may suppress PEL cells, given that SPKH leads to accumulation of sphingosine-1 phosphate (S1P) which activates antiapoptotic signal transduction; this approach was also effective on a mouse xenograft model of PEL (84). BET bromodomain inhibitors ((+)-JQ1 and I-BET151) have been tested in PEL, given that KSHV-encoded proteins, in particular LANA, can increase the levels of MYC (85). Bromodomain inhibitors induced growth inhibition and G0/G1 cell-cycle arrest, apoptosis and cellular senescence in PEL cells.

Multicentric Castleman's disease (MCD) and associated lymphomas—KSHV is present in approximately half of MCD cases from immunocompetent individuals and in almost all individuals with HIV and MCD (86). KSHV is present in B cells in the mantle zones, which can be numerous, coalesce and form microlymphomas or frank lymphomas. These infected cells are monotypic but polyclonal, expressing IgM λ (87). Lymphomas that occur in association with MCD differ from PEL in that they are negative for EBV, they and they are thought to arise from arise from naïve IgM lambda-expressing B cells rather than terminally differentiated B cells (56, 88). Another very rare KSHV-associated B cell

lymphoma entity has also been described, called germinotropic lymphoproliferative disorder, where germinal center B cells are co-infected with EBV and KSHV (89).

The constitutional symptoms in MCD are thought to be due to production of excess cytokines, including interleukin-6 (IL-6) which is markedly elevated in this disease. The KSHV encoded vIL-6 is also expressed and thought to contribute to MCD pathogenesis (90–92); expression of this viral cytokine has been reported to confer a worse prognosis (93). In addition, the expression of other KSHV lytic proteins in KSHV-associated MCD suggest that there is uncontrolled viral proliferation in this disease. More recently an IL-6-related systemic inflammatory syndrome, called cytokine KSHV inflammatory cytokine syndrome (KICS), was reported in patients with HIV and KS, but without a pathologic diagnosis of MCD (94, 95).

Relationship of HIV and B cell lymphomagenesis

In addition to the clear association with EBV and KSHV, the increased incidence of B cell lymphomas in HIV infected patients is thought to be related to disrupted immune surveillance to tumor antigens, genetic alterations, chronic antigenic stimulation, and cytokine dysregulation (96–100). Supporting a role for HIV beyond immunosuppression, a recent large study conducted by the Centers for AIDS Research (CFAR) Network of Integrated Clinical Systems found that the incidence of NHL is increased even in patients treated with combined antiretroviral therapy, and that HIV viremia is a continuous variable associated with NHL with a hazard ratio of 1.42 per log₁₀ copies/mL (101)**. This high NHL incidence was seen even in patients with CD4 cell counts of >200 cells/μL. Another study also documented the association of detectable viremia with the incidence cHL (102). Also consistent with a role of HIV is the report of the development of B cell tumors in transgenic mice with a 7.4-kb pNL4-3 HIV-1 provirus expressing p17, gp120 and nef but lacking a parts of the gag-pol region (rendering it replication incompetent) (103).

While HIV itself does not infect B cells, there is also biological plausibility that this virus promotes lymphoma development through secreted viral proteins (1). HIV-induces chronic B cell stimulation, which precedes the development of lymphoma and is likely critical (104–106). A number of reports have implicated specific HIV proteins in this B cell hyperplasia, including Tat (107), Nef (108) (109), Env gp120 (110), Env gp130 and Gag p17 (111). Together with Tat inhibitory effects on DNA repair mechanisms in B cells(112), which are undergoing rearrangement as somatic hypermutation, this B cell hyperproliferation is more likely to transform into a lymphoma.

Interactions between HIV viral proteins and those encoded by oncogenic herpesviruses have been documented, involving secretion or transmission of HIV proteins through structures like nanotubules or exosomes affecting properties of pre-lymphomatous or lymphoma B cells (reviewed in (1)) and illustrated in Figure 2. Two recent studies documented interesting interactions between HIV Nef and KSHV. Nef can synergize with KSHV vIL-6 and activate the AKT pathway leading to angiogenesis and tumor formation in a model of KS (113). The second study showed that the HIV-encoded protein Nef can regulate KSHV latency by inducing cellular miRNA 1258 (hsa-miR-1258) that directly targets a seed sequence in the 3' untranslated region of the mRNA encoding the major lytic switch protein of KSHV (RTA)

(114). HIV Nef had been shown to be secreted in exosomes (115) and also penetrate bystander, uninfected B cells (109), so it may have an effect in maintaining latency of EBV or KSHV-infected B cells that eventually become transformed.

Conclusion

EBV and KSHV encode a large number of proteins, but only a small proportion is expressed in infected lymphoma cells. Nevertheless, these proteins have been shown to be able to control cellular proliferation, suppress apoptosis and provide mechanisms for immune evasion using a surprisingly large variety of tricks. In addition, the increased incidence of B cell lymphomas in HIV infected individuals appears to go beyond the effect of immunosuppression, and some of the possible roles of HIV as an inducer of B cell lymphomas are starting to be appreciated. However, many studies have relied on artificial overexpression and cell culture systems, and more complex and accurate modeling is necessary to assess the role of HIV under accurate physiological and pathological conditions. Understanding the mechanisms of virus-mediated lymphomagenesis will reveal which viral proteins are essential for lymphomagenesis and identification of inhibitors of specific viral proteins should be feasible. In the meantime, understanding of how the virus interacts and activates specific cellular pathways has begun to lead to the use of inhibitors that will take advantage of specific vulnerabilities of virus infected tumor cells.

Acknowledgments

Dr Cesarman is funded by NIH grants R01-CA154228 and R01-CA103646, U01 CA-121947, 3P30CA008748 and R21EB016803.

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Key points

- Two oncogenic herpesviruses infect B cells and cause B cell lymphomas: EBV and KSHV.
- Individuals with HIV infection are at a greatly increased risk of lymphoma development, and these more frequently contain an oncogenic herpesvirus.
- HIV likely plays a role in lymphomagenesis beyond induction of immunosuppression.
- Many studies have revealed functions of viral proteins that are related to lymphomagenesis.
- This information is beginning to guide targeted therapies.

Figure 1.

Major patterns of EBV and KSHV latent gene expression in lymphoproliferative disorders. The main EBV latency patterns and the most common lymphoproliferative disorders in which these patterns are seen are illustrated. The KSHV proteins that are uniformly expressed in PEL and MDC are shown in the right. Modified from previously published figure in (40).

Figure 2.

Role of HIV in lymphomagenesis. HIV has effects in promoting lymphomagenesis through secreted proteins, which can be indirect by enhancing immunosuppression, B cell hyperplasia and genomic instability. HIV proteins can also have effects on KSHV viral latency and reactivation.

Table 1

Major EBV genes expressed during latency

EBV gene	Protein function	Expression pattern		
		Lat I	Lat II	Lat III
EBNA-1	<ul style="list-style-type: none"> Binds to the origin of replication of the EBV episome, which is required for replication of the virus DNA and its distribution to the daughter cells in proliferating cells. Is not presented by MHC class I molecules, so that EBV-positive B cells expressing only EBNA1 are not recognized by cytotoxic T cells. Transgenic mice have increased incidence of lymphoma alone, and in cooperation with MYC. May protect cells from P53 mediated apoptosis. 			
EBER-1 and EBER-2	<ul style="list-style-type: none"> These are short non-polyadenylated RNAs. Can induce the secretion of interleukin-10 (IL-10), which might stimulate growth of infected B cells and suppress cytotoxic T cells. Might mediate resistance of EBV-positive Burkitt lymphoma cells to interferon-alpha. Because of their abundance, in situ hybridization for EBER is for histological detection of EBV. 			
LMP-1	<ul style="list-style-type: none"> Most effects of LMP1 are caused by activation of the NFkB pathway. This signaling pathway is similar to that of CD40, which has a key role in the activation and differentiation of B cells. Functions as an oncogene; transgenic mice expressing the gene in B cells develop lymphomas. Inhibits apoptosis by upregulating expression of a number of cytokines and apoptosis inhibitory proteins. Induces AID up-regulation and genomic instability via Egr-1 (7). 			
LMP-2A	<ul style="list-style-type: none"> Has ITAMs in its cytoplasmic domain. These motifs are also present in the B-cell receptor (BCR) co-receptors CD79A and CD79B and transmit activating signals after BCR stimulation. Binds and thereby sequesters tyrosine kinases from the BCR, resulting in inhibition of BCR signaling, preventing unwanted antigen-triggered activation of EBV-positive B cells that would cause entry into the lytic cycle. However, LMP2A itself stimulates these tyrosine kinases to some extent, thereby mimicking the presence of a BCR and providing an important survival signal for B cells 			
EBNA-2	<ul style="list-style-type: none"> First virus protein to be expressed after infection of B cells in vitro. Essential for cellular transformation. Interacts with the transcription factor RBP-Jk, thereby mimicking the Notch signaling pathway. Regulates several virus genes, including for example, latent membrane protein 1 (LMP1) and LMP2A, and many cellular genes including MYC. Repressed BIK, a pro-apoptotic molecule, thereby protecting infected cells from TGF-β1-induced apoptosis(8). 			
EBNA-3A–C	<ul style="list-style-type: none"> EBNA-3A and 3C are essential for viral transformation of B cells EBNA-3 A, B and C associate with RBP-Jk and alter transcription. EBNA-3C together with EBNA2 activates the LMP1 promoter. 			

EBV gene	Protein function	Expression pattern		
		Lat I	Lat II	Lat III
	<ul style="list-style-type: none"> EBNA-3C can affect ubiquitination of RB1 and p27 affecting cell cycle control. <u>EBNA3C associates with p73 and may inhibit its function (9).</u> 			
EBNA-LP	<ul style="list-style-type: none"> Cooperates with EBNA2 to activate gene expression. 			

Note: Only papers published within the last year are referenced.

Table 2

Major KSHV genes expressed during latency

EBV gene	Protein function
LANA	<ul style="list-style-type: none"> • Essential for episome maintenance. • It interacts with many nucleosomal proteins including core nucleosomal histones as well as with histone H1 and HMGs. (17) • Binds and inactivates RB1 and TP53. • Can also bind and inactivate GSK3B, leading to activation of the beta-catenin pathway and MYC stabilization • Has transcriptional effects on a number of viral and cellular genes, including as IL-6, hTERT, Pim1, and the TGFbeta type II receptor • Interacts with full-length isoform TAp73a, as well as its dominant negative regulator DNp73a, and affects TAp73a stability and sub-nuclear localisation, as well as TAp73a-mediated transcriptional activation of target genes (18) • May induce expression of ubiquitin C-terminal Hydrolase-L1 (UCH-L1) in cooperation with RBP-Jκ (19) • Upregulates expression of Survivin and induces its phosphorylation on T32 which in turn upregulates the activities of histone acetyltransferases and deacetylases which leading to an increase in viral copy number in infected B-cells (20) • Antibodies useful for immunohistochemical diagnosis of KS, PEL and MCD
vCYC	<ul style="list-style-type: none"> • Functional cyclin that can associate with CDK6 and induce phosphorylation of RB1 and overcome cell-cycle arrest • Differs from the cellular cyclin D in its ability to promote degradation of the CDK inhibitor CDKN1B (p27Kip) when complexed with CDK6 • vCYC transgenic mice develop lymphomas only when bred with <i>TP53</i> knock-out mice • vCYC-CDK6 complexes can induce phosphorylation of nucleophosmin (NPM1) leading to genomic instability
vFLIP	<ul style="list-style-type: none"> • Homologous to the cellular FLICE/caspase 8 inhibitory proteins (cFLIPs), which can inhibit death receptor mediated apoptosis • vFLIP activates NF-κB through both the classical and alternative pathways by binding to IKKγ • Induces expression of numerous genes, which include anti-apoptotic genes and growth factors • Protects PEL cells from spontaneous apoptosis • Protects B cells from autophagy by binding to Atg3 • Induces IRF4, which in turn supports latency by inhibiting KSHV lytic reactivation (21). • vFLIP transgenic and conditional knock-in mice develop B cell malignancies when expressed in B cells, and vFLIP accelerates the development of MYC induced lymphomas
vIL6	<ul style="list-style-type: none"> • Viral homolog of cellular IL6 • Differs from IL6 in that it is selectively glycosylated and can bind IL6ST (previously called IL-6 receptor beta, or gp130) in the absence of IL6R (the high affinity IL6 receptor, also called alpha or gp80) to activate IL6-responsive genes and promote B-cell survival. • vIL6 can interact with IL6ST within the ER (22) • Expressed by a variable but significant proportion of latently-infected PEL cells as well as in MCD, and has also been shown to be expressed at low levels in during true latency • Since this is a secreted protein, it has paracrine effects on neoplastic and tumor-infiltrating cells. <p>In the ER, it interacts with protein vitamin K epoxide reductase complex subunit 1 variant 2 (VKORC1v2) and proapoptotic cathepsin D (CatD) (23).</p>
vIRF3	<ul style="list-style-type: none"> • While not a DNA-binding protein, it can be recruited to the interferon promoters via its interaction with cellular IRF-3 and IRF-7, stimulating their transcriptional activity • Prevents TP53 function in reporter assays. • Associates with the DNA-binding domain of p53, inhibits p53 phosphorylation on serine residues S15 and S20, and reduces DNA binding affinity (116). • antagonizes p53 oligomerization

EBV gene	Protein function
	<ul style="list-style-type: none">Expressed in PEL but not KSInhibits transcription of CIITA and MHC Class II, leading to decreased recognition of infected cells by CD4+ T cells (24).
Kaposins	<ul style="list-style-type: none">This complex region is transcribed potentially encoding three proteins, called Kaposin A, B, and CKaposin B seems to be expressed in KS and some PEL cell lines, but not othersKaposin B may have transforming functions, including activation of the p38 pathwayKaposin B can stabilize cytokine mRNAs through activation of MK2 blocking the decay of mRNAs with AU-rich elements (AREs) in their 3' untranslated region; AREs are present in cytokine mRNAs, so Kaposin B increases the production of pro-inflammatory cytokinesKaposin A may be transformingKaposin A signals by recruiting cytohesin 1 to the plasma membraneKaposin B can activate STAT3 by inducing imonophosphorylation at Ser 727 (25).