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Cancers associated with human gammaherpesviruses

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Abstract

Epstein-Barr virus (EBV; human herpesvirus 4; HHV-4) and Kaposi sarcoma-associated herpesvirus (KSHV; human herpesvirus 8; HHV-8) are human gammaherpesviruses that have oncogenic properties. EBV is a lymphocryptovirus, whereas HHV-8/KSHV is a rhadinovirus. As lymphotropic viruses, EBV and KSHV are associated with several lymphoproliferative diseases or plasmacytic/plasmablastic neoplasms. Interestingly, these viruses can also infect epithelial cells causing carcinomas and, in the case of KSHV, endothelial cells, causing sarcoma. EBV is associated with Burkitt lymphoma, classic Hodgkin lymphoma, nasopharyngeal carcinoma, plasmablastic lymphoma, lymphomatoid granulomatosis, leiomyosarcoma, and subsets of diffuse large B cell lymphoma, post-transplant lymphoproliferative disorder, and gastric carcinoma. KSHV is implicated in Kaposi sarcoma, primary effusion lymphoma, multicentric Castleman disease, and KSHV-positive diffuse large B cell lymphoma. Pathogenesis by these two herpesviruses is intrinsically linked to viral proteins expressed during the lytic and latent lifecycles. This comprehensive review intends to provide an overview of the EBV and KSHV viral cycles, viral proteins that contribute to oncogenesis, and the current understanding of the pathogenesis and clinicopathology of their related neoplastic entities.

Keywords

Kaposi sarcoma-associated virus/human herpesvirus 8; Epstein-Barr virus; Kaposi sarcoma; primary effusion lymphoma; multicentric Castleman disease; Burkitt lymphoma; nasopharyngeal carcinoma; post-transplant lymphoproliferative disease; LANA; K1; K15; EBNAs; LMP1; LMP2A

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Author contributions

K.W. and B.D. wrote the review. LW provided images of primary effusion lymphoma and J.R.M. provided images of multicentric Castleman disease. L.W. and J.R.M. edited the manuscript.

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Introduction

The human gammaherpesviruses Epstein-Barr virus (EBV; human herpesvirus-4 or HHV-4) and Kaposi sarcoma-associated herpesvirus (KSHV; human herpesvirus-8 or HHV-8) are etiologic agents of a specific set of lymphoid and non-lymphoid neoplasms [1]. Like other herpesviruses, EBV and KSHV are double-stranded linear DNA viruses that exhibit a biphasic lifecycle (i.e., lytic and latent forms). Infections tend to persist in the host. Both viruses are known to cause human cancers when the infected hosts are immunosuppressed. EBV infects ~90% of the world's adults and is considered an oncogenic viral agent for several distinct human neoplasms, including nasopharyngeal carcinoma (NPC) [2], Burkitt lymphoma (BL) [3], classic Hodgkin lymphoma (CHL) [4], EBV-positive diffuse large B cell lymphoma (EBV+ DLBCL) [5], DLBCL associated with chronic inflammation [6], plasmablastic lymphoma (PBL) [7], lymphomatoid granulomatosis [8], and subsets of post-transplant lymphoproliferative disorder (PTLD) [9], gastric carcinoma (GC) [10], and leiomyosarcoma [11]. Of note, EBV was the very first human tumor virus identified. KSHV is implicated in Kaposi sarcoma (KS) [12], primary effusion lymphoma (PEL) [13, 14], multicentric Castleman disease (MCD) [15], and KSHV-positive diffuse large B cell lymphoma [16]. The numerous neoplasms caused by EBV and KSHV are likely due to their large genomes that encode a myriad of viral genes, which in turn enable these viruses to express proteins that modify the cellular environment.

Viral life cycle and oncogenesis

The primary route of transmission for both EBV and KSHV is via bodily fluids including saliva [17–19]. The virus lifecycle can be delineated into two phases, latency and lytic replication (Figure 1). As the default viral lifecycle of EBV and KSHV, latency is key for these viruses to persist in the infected cells. During latency, the viral genomes assume a circular/ring structure known as an episome. The viruses are replicated during host cell division and then segregated into daughter cells [20]. Only few viral genes are expressed in the latent state and no virions are produced during the latent stage. In contrast, viral lytic replication occurs following reactivation from latency or following infection in some cell types depending on the virus. Infectious virions are produced as a result of lytic infection. During lytic replication, viral gene expression is highly orchestrated in three sequential phases, including the immediate early (IE), delayed early (DE), and late (L) phase. IE genes do not require protein synthesis to be expressed (indicating that host cell factors are capable of activating the promoters of IE genes) and most IE genes are viral transcription factors. DE gene expression is dependent upon protein expression but not DNA synthesis and DE genes e.g., DNA polymerase is involved in replication of the viral DNA. Finally, L genes are expressed after DNA synthesis. Late proteins generally encode viral capsid and envelope proteins, but also include tegument proteins that are able to function immediately upon infection.

Typically, in the immunocompetent host, EBV and KSHV persist in infected B cells for many years without causing noticeable pathology. However, such long-term viral persistence via latency is postulated to contribute to human cancer when the host becomes

immunocompromised. However, evidence suggests that certain lytic proteins are also involved through autocrine/paracrine effects that can enhance transformation [21–23].

Viral oncogenic signaling

EBV and KSHV have evolved to hijack multiple cellular signaling pathways involved in tumorigenesis and oncogenesis. Here we will focus on three major pathways modulated by viral proteins: i) phosphatidylinositol-4,5-bisphosphate 3 kinases (PI3K)/protein kinase B (Akt)/mammalian target of rapamycin (mTOR) pathway; ii) mitogen-activated protein kinase (MAPK) pathway; and iii) nuclear factor-κB (NF-κB) pathway (Figure 1). There is crosstalk amongst these pathways, adding to the complexity of the interplay between host cell factors and viral proteins [24–26]. We have decided to select the three pathways above because they are well-known in viral and non-viral oncogenesis and can be used to highlight the roles of EBV and KSHV oncoproteins. In addition to these three major pathways, there is a plethora of other cellular pathways perturbed by both viruses (e.g., Notch, Wnt/β-catenin, JAK/STAT, TGF-β, p53, Toll-like receptors, etc reviewed in [27–30], but they are beyond the scope of this review.

PI3K/Akt/mTOR pathway

There are four classes of PI3K (IA, IB, II, and III) [31]. Class IA and IB PI3Ks are heterodimeric proteins comprised of a regulatory subunit (p85α, p85β, p55α, p55γ and p50α) and a catalytic subunit (p110α, p110β, p110δ and p110γ) [32]. Classes IA and IB catalyze the conversion of phosphatidylinositol-4,5-bisphosphate (PIP2) into phosphatidylinositol-3,4,5-triphosphate (PIP3). This enables pleckstrin homology (PH)-domain containing proteins to localize to the plasma membrane [32]. As a phosphatase, phosphatase and tensin homology (PTEN) reverses the reaction, converting PIP3 back to PIP2 [33]. Loss of PTEN expression or function thus removes the brake on PI3K-mediated signaling. PIP3 recruits phosphoinositide-dependent kinase 1 (PDK1) to the plasma membrane, where PDK1 activates Akt by phosphorylation. By inhibiting tuberous sclerosis complex 2 (TSC2), Akt activates mTOR complex 1 (mTORC1), resulting in induction of protein synthesis [34]. In brief, mTORC1 phosphorylates p70 S6 kinase (S6KB1) and eukaryotic translation initiation factor 4E-binding protein 1 (4EBP1). The phosphorylation of p70 S6 kinase (S6KB1) leads to downstream phosphorylation of the S6 ribosome for protein translation. Phosphorylated 4EBP1 unleashes 4EBP1's inhibitory effect on eukaryotic initiation factor 4E (eIF4E) and this unlocks the cap-dependent translational machinery [35]. Thus, the PI3K/Akt/mTOR signaling axis activates biogenesis and cellular proliferation. mTORC1 signaling has also been shown to regulate lipid metabolism and autophagy [36]. Other Akt downstream effects also include promoting cell cycle progression via transactivation of *MYC* and *CCND1* genes and repressing apoptosis (by inhibiting pro-apoptotic proteins such as Fas ligands) [37, 38].

MAPK pathway

The MAPK pathway can be physiologically initiated by growth factors, cytokines, and various stress (e.g. heat, oxidation, and radiation) [39]. In this signaling cascade through a series of phosphorylation events, a stimulus activates MAPKK kinase (MAPKKK) [24],

which in turn activates a MAPK kinase (MAPKK). The activated MAPKK subsequently phosphorylates and activates a downstream MAPK. The activated MAPK ultimately translocates into the nucleus and activates various transcriptions factors. Through this signaling cascade, the signal is dramatically amplified. The four canonical MAPK families in mammalian systems include extracellular-signal-regulated kinase (ERK) 1/2, ERK5, c-Jun N-terminal kinase (JNK)/stress-activated protein kinase (SAPK), and p38 kinase [40]. For example, in the "classical" MAPK pathway, extracellular ligand (growth factor or cytokine) binds to a receptor (e.g., G protein-coupled receptor (GPCR)), which phosphorylates and activates the MAPKKK Raf. Phosphorylated Raf then phosphorylates and activates the MAPKK MEK1/2, which in turn phosphorylates and activates the MAPK Erk1/2. Activated Erk1/2 then activates the substrate p90 S6 kinase (RSK), which subsequently activates various transcription factors including AP-1 [24]. As mentioned above, RSK also activates S6 and eIF4B that are a part of the mTORC1 signaling. The MAPK signaling events are critical for cell proliferation, cell cycle regulation, migration, and survival [40, 41].

NF-κB pathway

There are two major NF-κB pathways, namely, the canonical/classical and non-canonical/alternative pathways. The transcription factor (p65/p50 heterodimer) in the canonical pathway is inactivated and cytoplasmically sequestered by an inhibitor of NF-κB (composed of KKα/IKKβ/IKKγ (IKKγ is also known as NEMO)). The classical NF-κB pathway can be stimulated by tumor necrosis factor (TNF), IL-1, Toll-like receptor ligands, B cell receptor, or T cell receptor [42]. This is followed by activation of IκB kinase (IKK) complex, which then phosphorylates and degrades IκB via ubiquitination and proteasomal degradation. This subsequently enables the NF-κB heterodimer to translocate into the nucleus, whereby it activates several genes that are important for cell proliferation, angiogenesis, and inflammation [43].

The non-canonical NF-κB pathway can be induced by lymphotoxin, receptor activator of NF-κB ligand (RANKL), CD40 ligand, and B cell activating factor of the TNF family [42]. The NF-κB heterodimeric complex here is RelB/p52 instead of p65/p50. The non-canonical pathway is repressed by p100 in lieu of IκBα. Similar to IκBα in the canonical pathway, proteasomal degradation of p100 frees the NF-κB complex from cytoplasmic sequestration, permitting downstream activation of the pathway [44]. This alternative pathway is important for secondary lymphoid organ establishment and maintenance [43].

Individual KSHV/EBV viral proteins that modulate the above three major signaling pathways are described in subsequent sections of this review.

EBV lytic cycle

In order to enter epithelial cells, the virus binds to αvβ integrins and ephrin A2 receptor on epithelial cells [45, 46]. The viral glycoprotein gp350/gp220 allows EBV to bind CD21 on B cells, and fusion is triggered by a complex composed of gH/gL (gp110/gp85) and gB (gp25) [47, 48]. Next, the viral capsid enters the cytoplasm through endocytosis, followed by transportation along the microtubule to the nuclear membrane [49], where the viral genome

is injected into the nucleus through the nuclear pore and viral replication ensues. Viral replication can also occur when EBV-infected cells are reactivated from latency (Figure 2).

The immediate early (IE) lytic genes BZLF1 (Zta or ZEBRA) and BRLF1 (Rta) initiate lytic EBV replication. EBV Zta has a preference for the CpG sequences on the methylated viral genome [50]. This results in upregulated expression of ~30 early lytic genes. Linear viral DNA is also replicated. EBV can be reactivated from latency by chemical or biological induction using reagents including 12-*O*-tetradecanoylphorbol-13-acetate (TPA), 5-aza-deoxycytidine (5-aza), calcium ionophore, sodium butyrate, histone deacetylase inhibitor, anti-immunoglobulin, hypoxia, or TGF-β [51].

Following infection of epithelial cells, EBV can subsequently cross the mucosa and spread into the blood stream to infect primary B cells and memory B cells.

EBV latent cycle (0, I-III)

Latency is established after a brief period of abortive lytic replication [52–55]. Viral latency is classified into 4 types (types 0, I, II, and III) based on the latent genes expressed (Figure 2, Table 1). During latency 0 (exemplified in healthy individuals), EBER-1, EBER-2, and miRNAs are expressed. EBER-1, EBER-2, BARTs, miRNAs, and EBNA1 are expressed during latency I (e.g., Burkitt lymphoma). Latency II (exemplified by nasopharyngeal carcinoma and classic Hodgkin lymphoma) additionally includes expression of LMP1, LMP2A, and LMP2B. In latency III (characterized by EBV-positive large B cell lymphoma and EBV-positive post-transplant lymphoproliferative disorder), EBNA2, EBNA3A, EBNA3B, EBNA3C, and EBNA-leading peptide (LP) are expressed in addition to the genes expressed in latency II. Latency is primarily observed in infected B lymphoblasts [56]. The critical roles of EBV lytic and latent cycles during oncogenesis is nicely described in a review by Münz [57].

EBV oncogenic viral proteins

Latent membrane protein 1 (LMP1)

LMP1 is frequently detected in nasopharyngeal carcinoma, classic Hodgkin lymphoma, Burkitt lymphoma, HIV+ lymphomas, EBV+ PTLD, and EBV+ gastric carcinoma [58–62]. LMP1 functions as a constitutively active tumor necrosis factor (TNF) receptor CD40. It has been shown to activate the MAPK, PI3K (Akt), c-Jun N-terminal kinase (JNK), epidermal growth factor receptor (EGFR), and NF-κB signaling pathways, which regulate cellular proliferation, cell cycle progression, motility, and anti-apoptosis via BCL2 expression [63] (Figure 1). The carboxyl-terminal activating regions 1 (CTAR1) and CTAR2, have been identified within the cytoplasmic carboxy terminal domain of LMP1 that activates NF-κB: CTAR1 recruits the TNF receptor–associated factors (TRAFs such as TRAF1/2 or TRAF3/5 heterodimers), which in turn activate NF-κB-inducing kinase (NIK) and inhibitor of κB kinase α (IKKα) leading to stimulation of the noncanonical NF-κB pathway, while also activating the canonical pathway [64–66]. CTAR1 also activates PI3K, which in turns activates Akt and glycogen synthase kinase 3β (GSK3β) [67]. CTAR2 recruits TRAF2 and TRAF6 using adapter molecules to activate the canonical NF-κB pathway [68].

LMP1 CTAR2 also activates c-Jun N-terminal kinase pathway by recruiting TRADD and TRAF2 [69, 70]. Furthermore, LMP1 downregulates the cyclin-dependent kinase inhibitors p27Kip1 and p16INK4a, as well as upregulates the inhibitor of differentiation 1 (Id1) and inhibitor of differentiation 3 (Id3), cyclin-dependent kinase 2 (CDK2), and retinoblastoma (Rb) [71–73].

LMP1 has transforming activity in epithelial cells, B cells, and fibroblasts *in vitro* [65, 74, 75]. Of note, activation of the PI3K-Akt pathway, but not NF-κB, is required for Rat-1 fibroblast transformation [76]. In NPC cells, LMP1 has been shown to inhibit necroptosis through targeting receptor-interacting protein kinase 1 (RIPK1) and RIPK3 ubiquitination [77]. In murine models, LMP1 expression induces B cell lymphoma [62].

Latent membrane protein 2A (LMP2A)

LMP2A maintains viral latency in infected B cells. LMP2A contains immunoreceptor tyrosine-based activation motifs (ITAM) that enable it to function like a B cell receptor (BCR) and activate PI3K/Akt pathway, via activation of the tyrosine kinases Src and Lyn and PY motifs [78–82] (Figure 1). It thus drives B-cell development and provides a survival signal for EBV-infected cells independent of BCR [82, 83]. Interestingly, a high level of LMP2A can block BCR expression and signaling by a dominant-negative effect [84, 85]. It effectively excludes BCR from lipid rafts and directs Lyn and Syk kinases away from the BCR and to the ubiquitin-proteasome degradation pathway [85–88]. LMP2A also enhances production of IL-10 by activating Bruton's tyrosine kinase (BTK) and signal transducer and activator of transcription 3 (STAT3) [89]. LMP2A interacts with many cellular proteins as highlighted in a review on the LMP2A signalosome [90].

LMP2A expression is frequently detected in NPC, HL, and EBV+ gastric carcinoma [91–93]. In a gastric carcinoma line, LMP2A overexpression can prevent apoptosis induced by TGF-β1 [94]. This appears to be due to up-regulation of survivin expression by LMP2A [95]. LMP2A transgenic mice were characterized by a lack of surface immunoglobulin rearrangement resulting in BCR-negative B-cells, and yet these B-cells developed and survived via LMP2A ITAM signaling without the need for normal BCR signaling [82, 96]. B-cells from the LMP2A transgenic mice were sensitive to apoptosis with specific inhibitors of Ras, PI3K, and Akt, suggesting that LMP2A activates these cellular molecules to enhance B-cell survival [97].

Epstein-Barr virus nuclear antigen (EBNA)1

EBNA1 protein is crucial for latency and replication of the EBV genome. It tethers the circularized EBV episomes via the latent origin *oriP* to the host chromatin during cell division [98–103]. Binding to host chromosomes is mediated by EBNA1's RG-rich residues, arginine-rich and glycine rich regions, its association with EBP2 and other proteins, and/or G-quadruplex RNA binding action [100, 104–108]. This enables episomal maintenance in latently infected B cells [109–111]. In addition, EBNA1 can also enhance cellular and viral gene expression by binding to various promoters [112, 113].

EBNA1 is known to exert an indirect effect on the canonical NF-κB signaling pathway by inhibiting IKK phosphorylation and nuclear translocation of p65 [114]. In addition, EBNA1

can interact with USP7 that modulates p53 and Mdm2 by preventing their degradation [115, 116]. EBNA1 can also lead to the disruption of promyelocytic leukemia (PML) nuclear bodies, resulting in destabilization of p53, inhibition of apoptosis, and impaired DNA damage repair [117]. By forming a complex with Sp1/Sp1-like proteins bound to their cis-element at the survivin promoter, EBNA1 up-regulates survivin and prevents apoptosis in EBV-infected B lymphoma cells [118]. EBNA1 also perturbs STAT1 and transforming growth factor-β (TGF-β) signaling [119].

Although some studies suggest a role for EBNA1 in tumor formation in murine models [120, 121], recent studies by Kang et al. [122, 123] did not find similar results in nude mice. It is possible that EBNA1's main roles are in maintenance of viral genomes and gene expression that are needed for tumorigenesis, but that it does not directly exert an oncogenic effect. Regardless, the consistent expression of EBNA1 in all EBV-associated cancers makes it an attractive potential therapeutic target [124]. There are numerous cellular proteins that interact with EBNA1 that we cannot extensively cover here, and interested readers are encouraged to explore them in [125].

In terms of disease relevance, EBNA1 expression was associated with significantly enhanced CD25 expression in the Hodgkin lymphoma cell line L428 that could translate into increased likelihood for lymphomagenesis in nonobese diabetic-SCID mice [126]. The level of EBNA1 expression correlated with Burkitt lymphoma cells survival by modulating apoptosis [127]. Furthermore, RNA interference/suppression of EBNA1 inhibited proliferation of EBV-positive Burkitt's lymphoma cells [128]. In NPC, EBNA1 altered protein expression involved in oxidative stress responses and metastasis [129]. EBNA1 can also degrade PML proteins leading to PML nuclear body loss in NPC and EBV+ gastric carcinoma [117, 130]. EBNA1 inhibitors have also been developed [124, 131, 132].

EBNA2 and EBNA leading peptide (EBNA-LP)

EBNA2 is critical and necessary for viral transformation and immortalization of primary B-cells [133–135]. Although it does not directly bind DNA, EBNA2 targets DNA through binding to the C-promoter binding factor 1 (CBF1) that interacts with RBP-Jκ, which also modulates DNA binding by Notch [136–138]. Thus, EBNA2 can functionally mimic dysregulated Notch1 [139, 140].

EBNA2 functions to activate host cell gene expression, including *MYC, CD21, CD23* [141–144]. *MYC* gene transactivation is thought to drive hyperphysiological B cell proliferation [145]. EBNA2 also transactivates viral latent genes via the promoters of LMP1, LMP2A, and LMP2B [146–153]. EBNA2 enhances transcription by recruiting transcription factors and cofactors through the activation domain as well as by association with hSNF5/INI1 and recruitment of the human SWI-SNF complex [154–156]. EBNA2 also upregulates transcription of *TET2* and physically binds to TET2 protein to demethylate genes important for B cell transformation [157]. Furthermore, EBNA2 can transcriptionally suppress the expression of immunoglobulin M expression [158]. In Burkitt lymphoma lines with t(8;14) translocation, expression of c-Myc is activated under the immunoglobulin chain locus, suggesting that EBNA2 uses the same mechanism to control both IgM and c-Myc expression [158].

EBNA-LP is transcribed along with EBNA2 and has been shown to cooperate with EBNA2 to cause G0/G1 transition during immortalization and to transactivate cellular genes (e.g., *RBP-Jκ*, *MYC*, *Pu.1*, and *EBF1*) and viral genes [159–161]. However, EBNA-LP transgenic mice did not show increased tumor development but exhibited dilated cardiomyopathy [162].

EBNA3 proteins (EBNA3A, EBNA3B, EBNA3C)

All three EBNA3 proteins can antagonize the effect of EBNA2 on viral gene transactivation [163–165]. EBNA3A and EBNA3C are important for inhibition of plasmacytic differentiation and induction of B cell transformation, as they have been shown to repress $p16^{INK4A}$ and $p14^{ARF}$ in lymphoblast lines [166]. EBNA3A can induce histone modifications of the chemokine genes, CXCL9 and CXCL10 [167, 168]. As a viral oncoprotein, EBNA3C can cooperate with activated Ras to immortalize and transform primary rodent fibroblasts and disrupt cell cycle checkpoint [169, 170]. EBNA3C has been shown to block p53-mediated apoptosis via different mechanisms including direct binding and inhibition of p53 and induction of Aurora kinase B [171–174]. Unlike EBNA3A and EBNA3C, EBNA3B is thought to be dispensable for B cell transformation *in vitro* [175, 176]. EBNA3A and EBNA3C can recruit cellular proteins such as chromatin remodeling factors e.g. RBP-Jκ, histone deacetylases, and CtBP leading to deregulated gene expression [177–183]. Additional details of EBNA3 proteins are reviewed in [184–186].

EBV-encoded small RNAs (EBERs)

EBERs (EBER1 and EBER2) are confined to the nucleus and the most abundant viral transcripts during EBV latency (> 1 million copies per infected cell), which allow for very sensitive detection of EBV infection using *in situ* hybridization on tissue [187–191]. The EBERs modulate cellular proliferation, cell survival, and production of cytokines/autocrine factors [192]. They have been shown to interact with cellular La protein and the ribosomal protein, L22 [193, 194]. EBERs were shown to contribute to IL10-induced growth, malignant phenotypes, and resistance to apoptosis in BL [192, 195]. In addition, EBERs have been shown to induce the expression of insulin-like growth factor 1 (IGF-1) in EBV-positive gastric carcinoma cells, and nasopharyngeal carcinoma-derived cells, IL-9 in EBV-infected T cells, and IL-6 in lymphoblastoid lines [196–199]. EBERs released from EBV-infected patient sera can activate signaling from Toll-like receptor 3 in EBV-transformed lymphocytes and peripheral mononuclear cells, thus activating the type I interferon response [200, 201]. Additional roles of EBERs in EBV infection, oncogenesis, and modulation of immunity are reviewed in [191, 202, 203].

KSHV lytic lifecycle

KSHV is known to infect multiple cell types, including epithelial cells, endothelial cells, and various hematopoietic cells such as B cells, T cells, dendritic cells, and monocytes [204–206]. Multiple cellular receptors have been discovered for KSHV entry. They include the cysteine transporter xCT, ephrin receptor tyrosine kinase A2, DC-SIGN, and integrins [207–211]. KSHV enters the host cells primarily through clathrin- or actin-mediated endocytosis [212]. The envelope glycoproteins gB, gH, and gL of KSHV are necessary for fusion of the viral and cell membranes [213, 214]. KSHV binding to integrin also stimulates focal

adhesion kinase (FAK) [215], which activates a host of downstream signaling cascades (including the PI3K/Akt and MAPK, and NF-κB pathways). These events are important for viral entry (e.g., PI3K), viral capsid transition along the microtubule by utilizing dynein motors to the nuclear membrane (e.g., PI3K), cell survival, and viral and host gene expression (e.g., MAPK and NF-κB) [216–220]. After the linear KSHV genomic DNA enters the nucleus through the nuclear core complex, it can be replicated via the lytic pathway or enter the latent state with the formation of viral episomal DNA.

Lytic replication is essential for the release and spread of KSHV to other cells (Figure 2, Table 2). The KSHV IE gene known as replication and transcription activator (RTA) is encoded by open reading frame (ORF)50. RTA alone is necessary and sufficient to initiate lytic replication [221, 222]. Alternatively, KSHV reactivation from the latent state can be triggered by caspase 3-dependent apoptotic stress, in the absence of RTA activity [223, 224]. KSHV can also chemically switch from latency to lytic replication by 12-*O*-tetradecanoylphorbol-13-acetate (TPA), valproic acid (VPA), and sodium butyrate (NaB) [225, 226]. Examples of oncogenic viral proteins in the lytic cycle include K1, K15, viral interleukin 6 (vIL-6), and viral G protein-coupled receptor (vGPCR).

There is good evidence that viral latent proteins play oncogenic roles, by inducing cellular proliferation, inhibiting apoptosis, and evading immunity. However, KSHV lytic viral genes have also been shown to contribute to oncogenesis, as use of the nucleoside analogue ganciclovir could markedly lower the risk of KS in acquired immunodeficiency syndrome (AIDS) patients [227]. It is postulated that during lytic infection, inflammatory and angiogenic factors are induced, exerting an autocrine/paracrine effect on proliferation.

KSHV latent lifecycle (Figure 2, Table 2)

During KSHV latency, a handful of viral genes are expressed including latency-associated nuclear antigen (LANA), viral cyclin (vCyclin), and viral FADD-like interleukin-1-beta-converting enzyme-inhibitory protein (vFLIP), Kaposin, and microRNAs. In addition, viral interleukin-6 (vIL-6), K1, and K15 are expressed at a low level. LANA is needed to maintain latent replication, by spatially linking the viral episome with host chromatin [228, 229]. LANA can also serve as a transcriptional modulator of multiple viral and cellular genes [230]. LANA also binds to the promoter of RTA and other lytic genes to shut off their expression [230]. Of note, latently infected tumor cells make up the majority of KS and PEL tumors, while MCD displays more lytic gene expression.

KSHV oncogenic proteins

K1

The K1 transmembrane protein is expressed at low levels during latency but at much higher levels during the lytic cycle [231]. Like the B cell receptor and EBV LMP2A, the cytoplasmic tail of K1 contains a functional ITAM for signal transduction [232–235]. Unlikely BCR signaling which is transient, K1 constitutively activates the PI3K (via its p85 regulatory unit)/Akt/mTOR pro-survival pathway [236–238] in the absence of ligand and blocks Fas induction of apoptosis in B cells that is dependent upon heat shock proteins [239,

240] (Figure 1). Like vGPCR, K1 expression stimulates production and release of VEGF. This provides a positive feedback loop to activate PI3K/Akt/mTOR signaling [232–235, 241] via the ITAM signaling domain of K1 [232–235]. To activate MAPK signaling, K1 phosphorylates SH2-containing signaling molecules such as spleen tyrosine kinase (Syk), which signals through the MEK1/2-ERK1/2 pathway and PLCγ2 to mobilize calcium, leading to downstream nuclear localization of NFAT and NFAT binding with AP-1 [235]. More recently K1 has been reported to bind the γ subunit of 5'adenosine monophosphate-activated protein kinase (AMPKγ1) which was important for K1's ability to enhance cell survival [237]. K1 oncogenicity was demonstrated by its ability to transform rodent fibroblasts [233] and immortalize primary human umbilical vein endothelial cells [241]. K1-expressing transgenic mice developed sarcomatoid tumor and/or lymphoma, thought to be mediated by activation of NF-κB and the B-cell transcription factor, Oct2 [242, 243].

K15

Similar to the K1 protein, K15 is a transmembrane viral protein. K15 activates the mitogen-activated protein kinase (MAPK) pathway, NF-κB pathway, and PLCγ1 through tumor necrosis factor receptor-associated factor 2 (TRAF2)'s interaction with its SH2-binding site [244, 245] (Figure 1). K15 shares signaling activities of both LMP1 and LMP2A [238, 244–246]. Like LMP2A, K15 can block BCR signaling [247]. It can bind to HAX-1 *in vitro* and *in vivo* to exert an antiapoptotic effect [248]. K15 has been shown to be important for viral lytic replication and is expressed in KS, PEL, and MCD [247–249].

Latency-associated nuclear antigen (LANA)

ORF73 encodes for LANA, which is crucial for maintaining the KSHV episome as well as promoting latent viral replication [250]. LANA binds to histones and this allows KSHV to tether the viral episomes to the host chromatin [14]. LANA has pleiotropic effects on various important cellular pathways, such as p53 [251], retinoblastoma-E2F [252], mitogen-activated protein kinase (MAPK) [252], c-Myc [253, 254], β-catenin/Wnt [255], and Notch [256] signaling. These various pathways have been implicated in oncogenesis. LANA-expressing transgenic mice developed B-cell hyperplasia reminiscent of MCD [257, 258]. Of note, only a subset of older LANA-expressing transgenic mice developed B cell lymphomas highlighting that although LANA can promote cell survival, it may need additional genetic alterations or other viral/cellular oncoproteins for lymphomagenesis [257].

LANA expression can be detected in KS, PEL, and MCD *in vivo* [259]. For clinical diagnostic purposes, immunohistochemistry for LANA protein is used to establish KSHV infection in its associated malignancies [250, 260, 261].

Viral cyclin (vCyclin)

vCyclin (ORF72) is a viral homologue of cellular cyclin D [262, 263]. Physiologically, cyclin D forms a complex with cyclin-dependent kinases (CDK)6 and CDK4 to phosphorylate Rb, resulting in the release of the E2F transcription factor. KSHV vCyclin interacts with cyclin-dependent kinase (CDK)6 and, to a lesser extent, other CDKs, to degrade CDK inhibitors, phosphorylate Rb and histone H1, and promote cell cycle progression [264–266]. Unlike cellular cyclin D1, vCyclin/CDK complexes are insensitive

to CDK inhibitors and can degrade the CDK inhibitor $p27^{Kip}$ [264, 267]. vCyclin/CDK6 complex can phosphorylate the histone chaperone, nucleophosmin leading to genomic instability [268]. vCyclin is also necessary to overcome replicative senescence in primary human lymphatic endothelial cells [269].

In the absence of p53, lymphomagenesis was noted in vCyclin transgenic mice, implicating p53 loss is important to expand neoplastic clones with vCyclin-induced aneuploidy [270, 271]. In KS, pro-apoptotic vCyclin/CDK6 complex can phosphorylate and inactivate Bcl-2, suggesting that in addition to cell proliferation, modulation of apoptosis in infected host cells may also be important for the development of Kaposi's sarcoma [266, 272].

Viral FADD-like interleukin-1-beta-converting enzyme-inhibitory protein (vFLIP)/K13

vFLIP/K13 (ORF71) blocks apoptosis induced by death receptors in KS lesions [273, 274] and PEL cells [275]. vFLIP structurally resembles the short form of cellular FLIP by not possessing the caspase-like domain of the long form of cellular FLIP. Mechanistically, vFLIP contains two death-effector domains to interact with the adaptor protein FADD, and this inhibits the recruitment and activation of the protease FLICE by the CD95 death receptor [273]. As a result, vFLIP-expressing cells can be protected from apoptosis induced by CD95 or other death domain-containing receptors [273]. vFLIP can promote cellular transformation through interaction of TRAF2 and TRAF4 that lead to activation of NF-κB that likely confers anti-apoptotic effect and pro-survival benefit [273, 275–277] (Figure 1). This also contributes to the spindle cell morphology and proinflammatory cytokine milieu as seen in KS [278]. In PEL cell lines, vFLIP can lead to constitutive activation of NF-κB and induction of cellular IL-6 expression by persistently phosphorylating and activating IKBα [279, 280]. In line with this, treatment of PEL cells in a murine system with an NF-κB inhibitor induced apoptosis, suppressed tumor growth, and prolonged survival [281]. Furthermore, by interacting with Atg3, vFLIP can prevent cell death from autophagy and this protective effect can be reversed using FLIP-derived short peptides that bind vFLIP and Atg3 [282]. Viral FLIP binds heat shock protein 90 (Hsp90), which is important for signaling and tumorigenicity [283]. Thus, targeting vFLIP could be a potential therapeutic option for KSHV-associated malignancies.

Transgenic mice expressing vFLIP exhibited B cell transdifferentiation and acquired expression of histiocytic/dendritic cell markers. These mice showed hematologic features typical of PEL and MCD [284]. vFLIP expression in endothelial cells of transgenic mice resulted in increased proinflammatory cytokine (e.g., IL6 and IL10) expression as well as aberrantly increased myeloid cells that might support a role in establishing the tumor microenvironment of various KSHV-associated lesions [285].

Viral G protein-coupled receptor (vGPCR)

vGPCR encoded by ORF74 is a chemokine receptor and cellular homologue of interleukin 8 (IL-8) receptors such as CXCR1 and CXCR2 [286–288]. Unlike its cellular homologue, vGPCR is constitutively active and does not respond to ligands [286–288]. As a viral oncoprotein expressed in the lytic cycle, vGPCR has been shown to transform endothelial cells and induce sarcomagenesis by hijacking the PI3K/Akt/mTOR pathway [289–293],

MAPK pathway [294, 295], and NF-κB pathway [288, 296, 297] (Figure 1). Specifically, vGPCR constitutively activates p44/p42 MAPK signaling and PI3K/Akt signaling [295]. The signaling activity of vGPCR results in phosphorylation of regulatory tyrosine residues in Shp2, which is required for vGPCR-mediated activation of MEK in the MAPK pathway, NF-κB, and AP-1 [288]. Through MAPK signaling, vGPCR can also stimulate HIF-1α transcription [294]. In addition, vGPCR has also been shown to activate the canonical β-catenin/Wnt pathway [298]. KSHV vGPCR activates Rac1 and VEGF, both important for KS angiogenesis via autocrine/paracrine growth factor secretion [294, 299, 300]. Transgenic expression of vGPCR induced KS-like angioproliferative disease in a mouse model [301–303]. Conversely, siRNA knockdown of vGPCR in a KSHV bacterial artificial chromosome (BAC) cell culture system inhibited angiogenesis and KS-like tumorigenesis [304]. These studies indicate a critical role of vGPCR in the pathobiology of KS.

Viral protein kinase (vPK)

vPK is encoded by ORF36 and its expression can be induced by a hypoxic environment [305, 306]. It is a nuclear protein with serine-threonine kinase activity [305]. Functioning as a cyclin-dependent kinase (CDK), vPK has been shown to phosphorylate retinoblastoma and lamin A/C proteins [307]. In addition, it can phosphorylate mitogen-activated kinases 4 and 7 (MKK4 and MKK7), thereby activating c-Jun N-terminal kinase (JNK) pathway [308]. KSHV vPK was reported to structurally and functionally mimic the cellular protein S6 kinase (S6KB1) [309]. For example, it can phosphorylate the ribosomal S6 protein and eukaryotic initiation factor 4E (eIF4E) downstream of the PI3K/Akt/mTOR pathway, resulting in enhanced global protein synthesis, anchorage-independent cellular proliferation, as well as endothelial tubule formation [309] (Figure 1). Transgenic vPK mice were prone to developing lymphoproliferative disorder and lymphoma of B cell origin [310].

Clinical Diseases associated with EBV and KSHV

Clinicopathologic presentation of human neoplastic diseases associated with EBV

Burkitt lymphoma—Burkitt lymphoma (BL) is a highly aggressive B cell lymphoma that tends to involve extranodal sites and patients can present with tumor lysis [311]. While highly proliferative, with a doubling time of about a day, BL is frequently curable due to its high sensitivity to chemotherapy. Intensive chemotherapy confers long-term overall survival in the vast majority of cases. EBV can be variably detected in the three clinical/epidemiologic BL variants (more than 95% in endemic BL, 20–30% in sporadic BL, and 30% in immunodeficiency-associated BL). EBV exhibits a latency I program in BL, expressing EBNA1, LMP2, EBER, and BART miRNA. *Endemic BL* is most common in children (male-to-female ratio of 2:1) in equatorial Africa and Papua New Guinea [3, 312, 313]. In addition to EBV, it is associated with polymicrobial infections with malaria and arboviruses [314–316]). Endemic BL involves facial bones (e.g., mandible and orbit) in more than 50% of cases. *Sporadic BL* has a low incidence and accounts for 1–2% of tumors in western countries. It tends to involve the abdomen but may also destroy facial structures. *Immunodeficiency-associated BL* is most common in the setting of human immunodeficiency virus (HIV) infection and often presents in the lymph nodes and bone

marrow. Its incidence has decreased since the introduction of highly active antiretroviral therapy (HAART) for HIV/AIDS[317].

Under the microscope, BL shows a diffuse proliferation of intermediate-sized lymphoid cells with round to mildly irregular nuclear contours, few nucleoli, deeply basophilic and often vacuolated and “squared off” cytoplasm. Scattered tingible-body macrophages are often noted in the background, imparting a “starry-sky” pattern (Figure 3, A–B). There tend to be many mitotic figures and apoptotic debris. The neoplastic cells express B cell antigens, such as CD20, PAX5, and CD79a. They demonstrate a germinal center phenotype (CD10 and BCL6 positive) and lack BCL2 [318, 319] (Figure 3, C–D). By definition, BL expresses c-Myc protein, which correlates with the rearrangement of the *MYC* oncogene at t(8;14), t(2;8), or t(8;22), and has a very high Ki-67 proliferative index by Ki-67 (virtually 100%) [319]. Next-generation sequencing frequently reveals mutations in *TCF3* (that modulates germinal center gene expression and B cell receptor signaling via the PI3K pathway) or its negative regulator *ID3* [320–322].

Classic Hodgkin lymphoma—Classic Hodgkin lymphoma (CHL) accounts for 90% of Hodgkin lymphomas. It exhibits a biphasic age distribution with the first peak at 15–35 years and second peak in older adult age. CHL tends to present with localized lymphadenopathy. Cervical lymph nodes are the most common affected (~75% of cases). Constitutional B-symptoms are noted in ~40% of patients.

In CHL, latency II is observed, with EBV expressing EBNA1, LMP1, LMP2, and EBER. The neoplastic Hodgkin/Reed-Sternberg (HRS) cells tend to be the minor population that is admixed in a background of inflammatory cells. HRS cells appear to have arisen from late germinal center or early postgerminal center B cells. These cells harbor crippling immunoglobulin genes rearrangements and would normally die, but they are rescued by NF-κB activation through LMP1 and LMP2 [83, 323, 324]. Furthermore, LMP1 induces Bmi-1 expression via NF-κB to provide a survival advantage for CHL [325].

Based on the inflammatory and fibrotic background, CHL has 4 different histologic subtypes: nodular sclerosis (NS), mixed cellularity (MC), lymphocyte-rich (LR), and lymphocyte-depleted (LD). EBV is detected more frequently in the mixed cellularity and lymphocyte-depleted subtypes than the nodular sclerosis and lymphocyte-rich subtypes [4]. EBV infection is implicated in blocking apoptosis in these cells. Hodgkin cells contain a single large nucleus with vesicular chromatin, a single large eosinophilic nucleolus, and abundant cytoplasm. Reed-Sternberg cells are binucleate/multinucleate with otherwise similar cytomorphology.

NS CHL is the most common CHL subtype in the United States and developed countries and accounts for 70% of cases. It is grossly and histologically characterized by thick fibrous bands surrounding nodules composed of inflammatory cells and neoplastic HRS cells. The inflammatory milieu frequently comprises eosinophils, neutrophils, lymphocytes, plasma cells, and histiocytes. EBV can be detected in neoplastic HRS cells in 10–25% of cases. Mixed cellularity (MC) subtype is the second most common subtype of CHL, accounting for 20–25% of cases. In patients with HIV, the MC subtype comprises the majority of all CHL

subtypes, especially as CD4 counts decrease [326]. The neoplastic cells are often positive for EBV (75% of cases) (Figure 3, E–J). It is also characterized by a polymorphous background, but prominent fibrous bands of the NS subtype must be absent. Lymphocyte-depleted (LD) subtype is the rarest subtype of CHL and tends to present at older age and late stage [327]. It has an abundance of HRS cells. Similar to the MC subtype, EBV is frequently present in HRS cells (~75% of cases) [327]. In the LR subtype of CHL, EBV is detected more frequently than the NS subtype but less commonly than the MC and LD subtypes. Regardless of histologic subtype, the HRS cells express strong diffuse CD30 and dim PAX5 in virtually all cases and CD15 in most cases [328, 329] (Figure 3, E–J). However, HRS cells have a downregulated B cell program and lack most other B cell markers, such as CD79a, OCT2, and Bob.1 that is thought be related to the reprogramming effect of LMP1 [330]. CD20 expression may be absent or present with variable intensities [328, 329, 331].

EBV-positive diffuse large B-cell lymphoma—EBV-positive diffuse large B cell lymphoma (DLBCL), not otherwise specified (NOS) was previously termed “EBV-positive diffuse large B cell lymphoma (DLBCL) of the elderly” by the World Health Organization (WHO) Classification of Tumours of Haematopoietic and Lymphoid Tissues [332–335]. It is thought to arise due to immunosenescence. EBV-positive DLBCL, NOS can present in lymph nodes or extranodally, such as the gastrointestinal tract or lungs [336]). It is clinically aggressive and has a poor prognosis compared to EBV-negative DLBCL [336–338], although younger ages confer much better prognosis [333]. The prevalence of EBV in DLBCL varies with age from 6.7% for individuals younger than 50 years old [334] to 20–30% in patients more than 90 years old [339].

By definition, this diagnostic entity is a large B cell lymphoma with EBV expression (Figure 4A). EBV-positive DLBCL exemplifies latency III, where EBNA1, LMP1, LMP2, EBER, EBNA2, and EBNA3A/3B/3C are expressed. It may contain some HRS-like cells or show histopathologic resemblance to PTLD, despite the fact that clinically there should be no history of immunosuppression. By immunohistochemistry, the lymphoma cells express pan-B cell markers such as CD20, PAX5, and CD79a (Figure 4, B–D). They show non-germinal center phenotype (e.g., CD10 negative, BCL6 positive, and MUM1) [333, 340, 341]. They can be CD30-positive but CD15 is usually negative. *In situ* hybridization for EBV is positive in numerous lymphoma cells.

Another type of DLBCL associated with EBV is termed DLBCL associated with chronic inflammation. The transformation and proliferation of EBV-positive cells are thought be stimulated by cytokine-mediated local immunodeficiency as a result of prolonged chronic suppuration/inflammation within a restricted anatomic space. The prototypic type of this aggressive lymphoma is pyothorax-associated lymphoma (PAL), a heavily male predominant disease that has been most frequently reported in Japan [6, 342]. Other body cavities can be involved by DLBCL associated with chronic inflammation. The morphological and immunophenotypic features of DLBCL associated with chronic inflammation are similar to those of EBV-positive DLBCL.

Plasmablastic lymphoma—Plasmablastic lymphoma (PBL) is a highly aggressive large B cell type lymphoma with plasmacytic differentiation. It arises in the setting of

immunodeficiency. It most frequently occurs in HIV/AIDS individuals but is also present in other immunosuppressive states including autoimmune therapy, transplant therapy-related immune suppression, and immune senescence [7, 343, 344]. The prognosis is poor with a median survival of less than 1 year [345, 346]. EBV is quite frequently detected in the neoplastic cells. Clinically, PBL commonly presents as an extranodal mass, with the oral cavity/head and neck region being the most common site (44% of PBL), followed by the gastrointestinal tract mucosa (14% of PBL). [347]. Nodal involvement is much less common (7% of all PBL) but is the most common site of PBL presentation in the post-transplant setting [345, 348]. Of note, a small subset of cases has been reported in immunocompetent individuals [347]. Latency I is typically noted in PBL with EBV expressing EBNA1 and EBER; however, latency III can be seen in those patients with HIV infection or posttransplant PBL [345]. PBL is treated aggressively with CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) chemotherapy regimen and/or radiation [345]. In an AIDS-associated PBL cell line, IL-6 dependence on cell survival and proliferation was observed, with apoptosis induced by an mTOR inhibitor [349].

On microscopic examination, PBL has two morphologic variants: 1) “monomorphic” variant composed predominantly of immunoblasts with prominent single nucleoli and minimal to no plasma cell differentiation and 2) “plasmacytic” variant with marked plasmacytic differentiation. PBL is a very aggressive lymphoma, with high mitotic activity and a proliferative index measured by Ki-67 labeling is >90%, and karyorrhexis is often noted (Figure 4, E–F). Numerous tingible body macrophages with a starry-sky pattern are quite common. The large neoplastic cells have a plasma cell immunophenotype. They are positive for CD138, MUM1, CD38, BLIMP-1, and CD79a (weakly positive in ~50% of cases) [347, 350] (Figure 4, G–J). In 75% of the cases, *in situ* hybridization for EBER is positive, whereas LMP1 antigen is negative (EBV latency type 1), although rare cases do express LMP1 (EBV latency type 3) typically in the HIV-positive or post-transplant settings [345]. Unlike “HHV-8/KSHV positive large B-cell lymphoma”, KSHV is negative in all cases of PBL [347, 351]. PBL is typically negative or very weak for the B cell antigens CD20, CD22, and PAX5. These features help distinguish PBL from diffuse large B cell lymphoma, which should express several markers of B-cell lineage. Other markers that are frequently expressed in PBL cells are c-Myc (which is related to *MYC* gene rearrangement), CD30, and epithelial membrane antigen (EMA).

Nasopharyngeal carcinoma—Nasopharyngeal carcinoma (NPC) has a high prevalence in southeast Asia and the southern part of China [352]. It is most common in the 4th to 6th decade with a male predominance (male-to-female ratio of ~ 2–3:1). NPC tends to metastasize to locoregional lymph nodes [353]. The 5-year overall survival for stage IV is about 75%. It is a squamous cell carcinoma arising in the nasopharynx and has a very strong association with EBV infection (>95%) with an increasing incidence in the United States [2, 354]. Other risk factors include dietary intake of nitrosamine in fermented salt-preserved food, cigarette smoking, and exposure to radiation or chemicals such as formaldehyde in the occupational setting [355, 356]. Prognostic factors include older age, male gender, cranial nerve involvement, metastatic disease, high serum lactate dehydrogenase prior to therapy, certain HLA types, EGFR overexpression, and high neutrophil-to-lymphocyte ratio. NPC is

clinically treated with radiation and/or chemotherapy [357]. In NPC, EBV exhibits a latency II program, expressing EBNA1, LMP1, LMP2, EBER, BART miRNA, but LMP1 protein expression can be absent in some cases (likely related to the BART miRNA interaction with the nonterminal region of LMP1) [358–360].

Interestingly, expression of LMP1 can promote epithelial–mesenchymal transition via its positive effect on Snail that suppresses E-cadherin expression and may predict metastasis of NPC [361]. As a potential immunotherapy for NPC, EBV-specific cytotoxic T cell (CTL) lines can be generated from NPC patients, which showed promising safety and antitumor activity with good clinical responses [362].

Microscopically, syncytial neoplastic cells in nests, sheet, or dispersed tumor cells with the morphology of keratinizing (WHO type I) or nonkeratinizing (WHO type II) squamous cell carcinoma are present (Figure 5A). The nonkeratinizing type is strongly associated with EBV. The neoplastic cells have large nuclei, vesicular chromatin, and prominent nucleoli. Mitotic figures are present. They are often accompanied by reactive lymphoplasmacytic infiltrate (Figure 5A). The neoplastic cells show strong reactivity to squamous markers, including cytokeratin (CK) 5/6, p63, and p40 [363] (Figure 5, B–D). Markers for epithelial differentiation/carcinoma, including AE1/3 and CAM5.2, are also positive.

NPC is characterized by latent expression of EBNA1, LMP1, LMP2, EBER, and BART miRNA. *In situ* hybridization for EBER is very sensitive for highlighting the neoplastic cells (Figure 5C) but is negative in the background lymphocytes and plasma cells [364, 365].

Post-transplant lymphoproliferative disorder—EBV-positive post-transplant lymphoproliferative disorder (PTLD) exemplifies latency III, with expression of EBNA1, EBNA2, EBNA3A/3B/3C, LMP1, LMP2, and EBER. PTLD is a lymphoid proliferation that arises from immunosuppression in the setting of solid organs or hematopoietic stem cell (HSC) transplantation. It more commonly occurs within the first year after transplantation. Of note, solid organ transplantation (host-derived PTLD) has a higher risk for PTLD than HSC transplantation (donor-derived PTLD). The risk factors include negative EBV serostatus in the transplant recipients, type of allografts (e.g., incidence rate of ~20% in intestinal organ recipients versus 2% in renal organ recipients), pediatric population, and intensity/type of immunosuppressive agents [366]. Many cases (>90%) are serologically EBV-positive. Interestingly, EBV-negative cases tend to occur later, ~ 4–5 years post-transplant, and have a worse prognosis [367, 368]. Some EBV-negative PTLD cases were shown to be KSHV associated [369–371]. The clinical presentation and symptomatology are variable and include constitutional symptoms (such as fatigue, fever, and weight loss) and lymphadenopathy, likely related to involvement site (e.g., nodal vs. extranodal) and PTLD type.

Pathologically, PTLD is quite heterogeneous and includes 4 major categories per the current WHO classification. They include non-destructive PTLD and destructive PTLD (further subclassified into polymorphic, monomorphic, and classic Hodgkin lymphoma PTLD). Non-destructive PTLD has preserved tissue architecture and includes plasmacytic hyperplasia,

infectious mononucleosis, and florid follicular hyperplasia PTLD. Non-destructive PTLD generally responds well to attenuation or cessation of immunosuppressives.

By definition, polymorphic PTLD does not fulfill the criteria for any lymphoma or plasma cell neoplasm. Instead, it displays a full range of B cell maturation, from immunoblasts to plasma cells (Figure 5, H–J). The atypical cells are predominantly small to intermediate-sized lymphoid cells, but occasional larger cells and HRS-like cells may be present. Monomorphic PTLD consists of transformed cells typically at one stage of maturation and is classified according to the WHO-defined lymphoma or plasma cell neoplasm it most recapitulates. The most common form is diffuse large B-cell lymphoma (DLBCL) (Figure 5, E–G), which is followed by NK/T cell lymphoma, plasma cell neoplasm, and classic Hodgkin lymphoma. Monomorphic DLBCL type can have plasmacytic differentiation and HRS-like cells that impart some polymorphic appearance; however, the predominant cells should be transformed large cells. For monomorphic B cell PTLD, the atypical lymphoid cells are positive for the B cell markers (such as CD20, PAX5, and CD79a) and show frequent expression of CD30 (Figure 5, E–G). EBER stain is very useful to detect EBV status in tissue for clinicopathologic assessment of PTLD (Figure 5J). In EBV-positive cases, PTLD tends to show non-germinal center phenotype. By contrast, EBV-negative cases usually have a germinal center phenotype. Almost all cases of destructive PTLD have clonal immunoglobulin gene rearrangement, which is usually not detected in non-destructive PTLD. Polymorphic PTLD tends to be driven largely by EBV, whereas monomorphic PTLD may have secondary driver genetic alterations [372–375]. Most polymorphic PTLD and a smaller subset of monomorphic PTLD may regress with reduction of immunosuppressive regimen. With more localized presentation, surgery and/or radiation therapy may be given to the patients. For more persistent/refractory cases, anti-CD20 therapy (rituximab) or R-CHOP (rituximab-CHOP) can be used. It is unclear why a subset of PTLD (20–40%) are EBV negative. It may be related to technical difficulties, other viral (e.g., KSHV) or antigenic induction of PTLD, or loss of EBV after transformation (“hit-and-run” hypothesis) [368, 370, 371, 376].

Extranodal natural killer (NK)/T cell lymphoma, nasal type—Like CHL, latency II is observed in extranodal NK/T cell lymphoma, nasal type. Expression of EBNA1, LMP1 (variable), LMP2, and EBER is often observed. Extranodal NK/T cell lymphoma, nasal type is the most common lymphoma in the sinonasal tract [377]. It is most frequently seen in Asia, but also common in Mexico and South American countries [377, 378]. There is a male predominance. The typical presentation is a low-stage locally destructive lesion in the nasal cavity involving maxillary sinuses and palate of older patients. EBV-encoded small RNA is detected in virtually all cases [378]. Interestingly, a low viral titer in serum or tissue is associated with a more favorable prognosis. Survival is approximately 25–50% at 5 years.

Pathologically, the neoplastic cells display variable sizes with vesicular chromatin and prominent nucleoli. Increased mitotic figures and angiocentricity or angioinvasion growth patterns are often present (Figure 6, A–C). Increased expression of cell adhesion molecules and chemokine receptors has been observed and correlated with LMP1 expression, highlighting its putative role in angiogenesis [379]. There is also a polymorphic inflammatory infiltrate and necrosis [378, 380]. *In situ* hybridization staining for EBV-

encoded small RNA can help highlight the neoplastic NK/T cells (Figure 6D). The neoplastic cells are often diffusely positive for CD56 and the cytotoxic markers such as TIA-1, granzyme B, and perforin [378, 380] (Figure 6, E–H).

Gastric carcinoma associated with EBV—Gastric carcinoma with lymphoid stroma is also known as medullary carcinoma or lymphoepithelioma-like carcinoma. This is a rare subtype of gastric adenocarcinoma that is associated with EBV and accounts for 10% of all gastric carcinoma [381, 382]. It shows a male predominance and a predilection for arising in the proximal stomach [383]. The mean patient age is 60 years. EBV positivity in gastric carcinoma is associated with a more favorable prognosis compared to EBV-negative cases [384]. Gastric carcinoma associated with EBV is characterized by type II latency and typically expresses EBNA1, LMP1, LMP2A, and EBER.

The tumor can be grossly ulcerated or saucer-like with thickened wall. The neoplastic epithelial cells often proliferate in sheets and are associated with dense lymphoid infiltrate and intraepithelial lymphocytes (Figure 6I). The inflammatory background is composed of lymphocytes, histiocytes, neutrophils, and plasma cells and likely related to the immunogenic effects of EBV infection. The neoplastic cells contain abundant amounts of cytoplasm, enlarged nuclei, vesicular chromatin, and often prominent nucleoli. Interestingly, approximately one third of gastric carcinoma with lymphoid stroma cases are positive for EBV-encoded small RNA [385] (Figure 6J).

Clinicopathologic presentation of human neoplastic diseases associated with KSHV

Kaposi sarcoma—Kaposi sarcoma is an endothelial neoplasm. This is different from primary effusion lymphoma and multicentric Castleman disease, which are lymphoproliferative disorders of B cell origin. All the neoplastic endothelial cells are infected by KSHV [386, 387]. The classic presentation of Kaposi sarcoma (KS) is that of an elderly Mediterranean man ("*classic KS*"). *AIDS-associated KS* is the most common and aggressive form currently, although the advent of antiretroviral therapy for AIDS has reduced its incidence [388]. Other forms include *endemic KS* (e.g., children or African descents) and *post-transplant/iatrogenic KS*. Like PTLD, reduction of immunosuppressives may be efficacious for *iatrogenic KS*. KS lesions can involve skin, mucous membranes, and visceral organs. They often present as violaceous patches, plaques, or nodules. Interestingly, the mTOR inhibitor rapamycin showed dramatic KS remission in transplant recipients, highlighting the importance of activating the PI3K/Akt/mTOR pathway by viral oncoproteins in KS tumorigenesis [389, 390].

Histologically, KS is characterized by proliferation of spindle-shaped endothelial cells forming slit-like vascular spaces (Figure 7A). Extravasated red blood cells with hemosiderin and associated inflammatory cells can often be identified. Immunohistochemistry for LANA protein highlights KSHV-positive cells with classic speckled/punctate nuclear staining pattern. The endothelial origin can also be confirmed by immunohistochemistry for vascular markers such as ERG (Figure 7, B–D).

Primary effusion lymphoma—Primary effusion lymphoma (PEL), also known as body cavity-based lymphoma, is a highly aggressive and fatal disease that is mainly seen in

severely immunocompromised AIDS individuals [387, 391, 392]. All cases are high stage and patients have a median survival of less than 6 months [393]. The lymphoma is typically seen in body cavities (e.g., pleural, pericardial, and peritoneal effusion fluids) but it can also present as an extranodal mass (so-called extracavitary or solid variant). [391, 394, 395]. Additionally, these patients may have concurrent KS or multicentric Castleman disease [391, 396, 397]. PEL cells are of post-germinal center origin. By definition, the neoplastic cells are KSHV-positive. Indeed, PEL cells harbor KSHV genome at a high copy number (50–150 per cell) [394]. Many KSHV latent products such as LANA, vCyclin, vFLIP, Kaposin, vIRF3 can be detected in PEL cells. Coinfection with EBV is commonly detected, particularly in the HIV setting, therefore, EBV is likely a cofactor, but is not causative [398, 399]. PEL cells are highly addicted to the PI3K/Akt/mTOR and MAPK pathways, and single or dual inhibitors of these kinases were tested *in vitro* which showed promising results [26, 400, 401]. The proteasome inhibitor bortezomib targets the NF-κB pathway and was found to be efficacious by inducing apoptosis in PEL cells [402–404]. More recently, inhibitors of fatty acid synthase and sphingosine kinase 2 also induced apoptosis in PEL cells, suggesting the potential therapeutic relevance of targeting dysregulated pathways of metabolism [405, 406].

Histologically, PEL cells are large sized with pleomorphic nuclei, prominent nucleoli, and abundant amounts of basophilic/amphophilic cytoplasm with or without vacuoles (Figure 7, E–F). They may resemble plasmablasts, immunoblasts, or occasional Hodgkin/Reed-Sternberg cells (binucleated/multinucleated forms). Stains for KSHV (LANA and viral IL-6) and EBV (e.g., *in situ* hybridization for EBV-encoded RNA) are useful, with detectable EBV co-infection in about half of the cases [398, 399]. They are often negative for B cell markers (CD20, PAX-5), but can be detected by CD45 and plasmacytic markers (CD138, CD38, MUM1, EMA) [395, 407] (Figure 7, G–J). Increased c-Myc expression is also a known phenomenon and has been shown to be driven by KSHV LANA [253, 254].

Multicentric Castleman disease—Multicentric Castleman disease (MCD) is also called multicentric angiofollicular hyperplasia. Clinically, the patient often shows systemic symptoms, including fever, night sweats, weight loss, generalized lymphadenopathy, hepatomegaly, splenomegaly, and autoimmune phenomena. Interestingly, serum interleukin-6 (IL-6) can be detected, at least in part, due to the effect of viral IL-6 and LANA [408]. The plasma cell variant of MCD has a very strong association with KSHV infection, especially in the AIDS setting [15, 387]. Tocilizumab and siltuximab, both monoclonal antibodies against human IL-6 receptor, have been investigated to treat MCD and found to produce clinical responses without severe toxicities or complications [409–412]. Unlike KS and PEL, KSHV lytic proteins are more commonly expressed in MCD [413]. A small pilot study investigated the utility of targeting the two KSHV lytic genes ORF36 and ORF21, using zidovudine and valganciclovir in KSHV+ MCD, showed promising clinical responses and survival [414]. This highlights the potential of targeting lytic KSHV infection in KSHV-associated MCD.

Morphologically, the lymph node shows extensive vascular proliferation in the germinal centers. Plasma cells and plasmablasts are increased in the mantle zones and interfollicular areas (Figure 7, K–N). Atypical plasmacytoid cells known as plasmablasts in the mantles

are often present and they are often monotypic for IgM heavy chain and lambda light chain expression (Figure 7, K–N).

HHV-8/KSHV-positive diffuse large B-cell lymphoma, NOS—Large B-cell lymphomas can be positive for KSHV LANA antigen and found in patients with a systemic KSHV infection [16, 351, 407, 415, 416]. They are termed “HHV-8/KSHV-positive diffuse large B-cell lymphoma, NOS” [16]. They most commonly arise from MCD, and the patients often present with splenomegaly as well as other KSHV-associated lesions such as KS and PEL [351, 396, 397, 415]. However, they can occasionally be seen without evidence of MCD [407, 415]. The neoplastic cells efface the architecture of the involved lymph node, spleen, or other sites such as marrow and peripheral blood [16, 351, 416]. They morphologically resemble plasmablasts (or immunoblasts); they are positive for LANA, cytoplasmic IgM, and lambda light chain but negative for CD45 and CD20 [16, 351, 407, 416]. However, immunoblastic morphology has also been reported. These patients often have other KSHV-associated lesions such as KS and PEL [396, 397].

Finally, KSHV and EBV have been concurrently associated with germinotropic lymphoproliferative disorder [415, 417], which is not associated with HIV/AIDS and is not considered a malignant neoplasm. It is thus not further discussed in this review.

Concluding remarks

Both KSHV and EBV are oncogenic gammaherpesviruses that are implicated in several human neoplastic diseases. Oncogenesis by either virus is related to the viral oncoproteins of the lytic and latent states that are both crucial for the viruses to replicate, propagate, and persist in in a lifelong manner. These viral proteins function by perturbing physiologic signaling pathways, thereby enhancing pro-survival, anti-apoptotic, and immunoevasive properties of EBV and KSHV. As highlighted in this review, animal models have generated very informative data for understanding the oncogenic properties of these viral proteins *in vivo*. The neoplastic diseases seen in mouse models appear to mirror the histopathology observed in the human counterparts. Although current mainstay therapies do not target the lifecycles and viral proteins of EBV and KSHV, rational design of drugs and vaccines that prevent viral entry into specific cell types, lytic and latent replication, and the oncogenic and immune evasive function of various EBV and KSHV proteins may enable more effective prevention and treatment of the human cancer associated with these viruses.

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Abbreviations:

4EBP1	4E-binding protein 1
5-aza	5-aza-deoxycytidine
AIDS	acquired immunodeficiency syndrome

Akt	protein kinase B
BL	Burkitt lymphoma
BTK	Bruton’s tyrosine kinase
CDK	cyclin-dependent kinase
CHL	classic Hodgkin lymphoma
CHOP	cyclophosphamide, doxorubicin, vincristine, prednisone
CK	cytokeratin
DE	delayed early
DLBCL	diffuse large B cell lymphoma
EBNA	Epstein-Barr virus nuclear antigen
EBERs	EBV-encoded small RNAs
EBV	Epstein-Barr virus
EGFR	epidermal growth factor receptor
eIF4E	eukaryotic initiation factor 4E
ERK	extracellular-signal-regulated kinase
GC	gastric carcinoma
GPCR	G protein-coupled receptor
HAART	highly active antiretroviral therapy
HHV-4	human herpesvirus 4
HHV-8	human herpesvirus 8
HIV	human immunodeficiency virus
HRS	Hodgkin/Reed-Sternberg
HSC	hematopoietic stem cell
IE	immediate early
Ig	immunoglobulin
IL	interleukin
ITAM	immunoreceptor tyrosine-based activation motifs
JNK	c-Jun N-terminal kinase
KSHV	Kaposi sarcoma-associated herpesvirus

L	late
LANA	latency-associated nuclear antigen
LD	lymphocyte-depleted
LMP	Latent membrane protein
LR	lymphocyte-rich
MAPK	mitogen-activated protein kinase
MC	mixed cellularity
MCD	multicentric Castleman disease
MKK	mitogen-activated kinase
mTOR	mammalian target of rapamycin
NaB	sodium butyrate
NF-κB	nuclear factor-κB
NK	natural killer
NPC	nasopharyngeal carcinoma
NS	nodular sclerosis
ORF	open reading frame
PAL	pyothorax-associated lymphoma
PDK1	phosphoinositide-dependent kinase 1
PBL	plasmablastic lymphoma
PEL	primary effusion lymphoma
PH	pleckstrin homology
PI3K	phosphatidylinositol-4,5-bisphosphate 3 kinase
PIP2	phosphatidylinositol-4,5-bisphosphate
PIP3	phosphatidylinositol-3,4,5-triphosphate
PTEN	phosphatase and tensin homology
PTLD	post-transplant lymphoproliferative disorder
RANKL	receptor activator of NF-κB ligand
Rb	retinoblastoma
R-CHOP	rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone

RSK	p90 S6 kinase
RTA	replication and transcription activator
S6KB1	p70 S6 kinase
SAPK	stress-activated protein kinase
STAT3	signal transducer and activator of transcription 3
TGF-β	transforming growth factor-β
TNF	tumor necrosis factor
TPA	12-O-tetradecanoylphorbol-13-acetate
TRAF	tumor necrosis factor receptor-associated factor
TSC2	tuberous sclerosis complex 2
vCyclin	viral cyclin
vFLIP	viral FADD-like interleukin-1-beta-converting enzyme-inhibitory protein
vGPCR	viral G protein-coupled receptor
vIL-6	viral interleukin 6
VPA	valproic acid
WHO	World Health Organization

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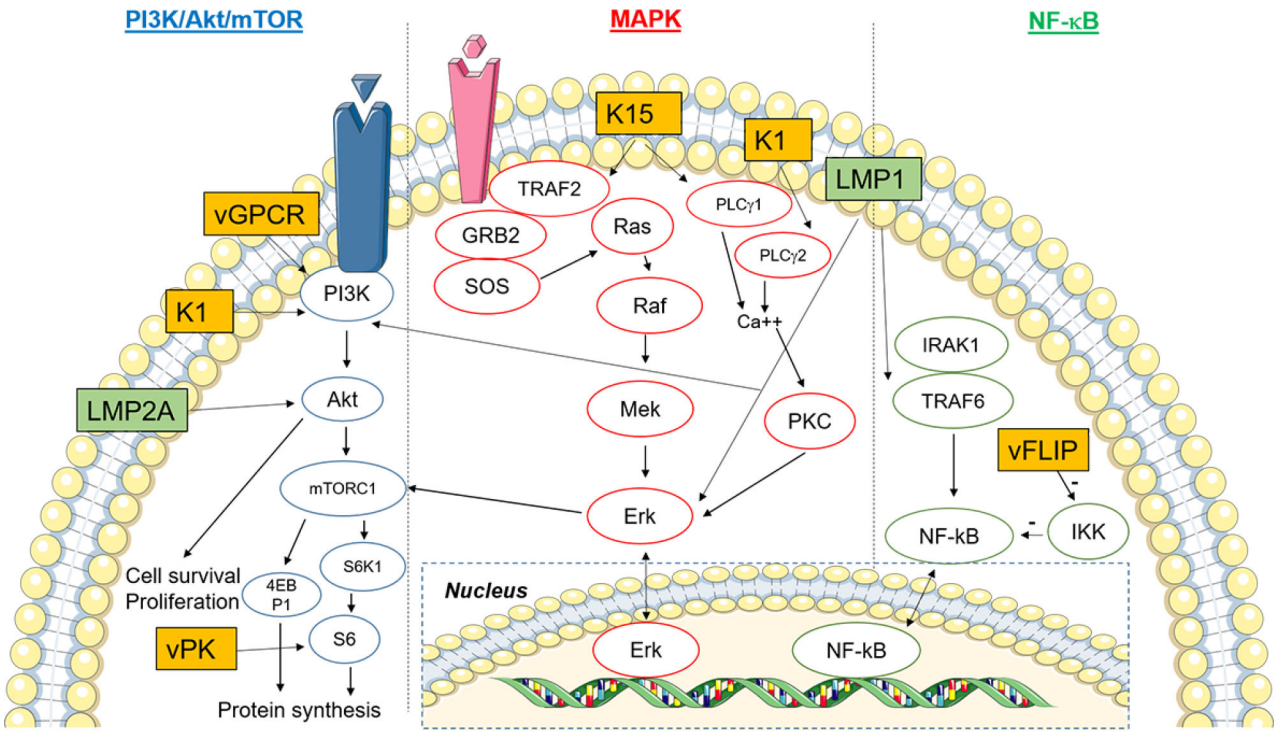

Figure 1.

Key signaling pathways modulated by Epstein-Barr virus (EBV) and Kaposi sarcoma-associated virus (KSHV) proteins. The pathways shown include PI3K/Akt/mTOR, MAPK, and NF-$_K$B. KSHV oncoproteins (K1, K15, vGPCR, vFLIP, vPK) are in orange boxes, whereas EBV oncoproteins (LMP1, LMP2A) are colored green. Please refer to the main text for detailed description of these pathways. Figure was created using artwork images from https://smart.servier.com/image-set-download/.

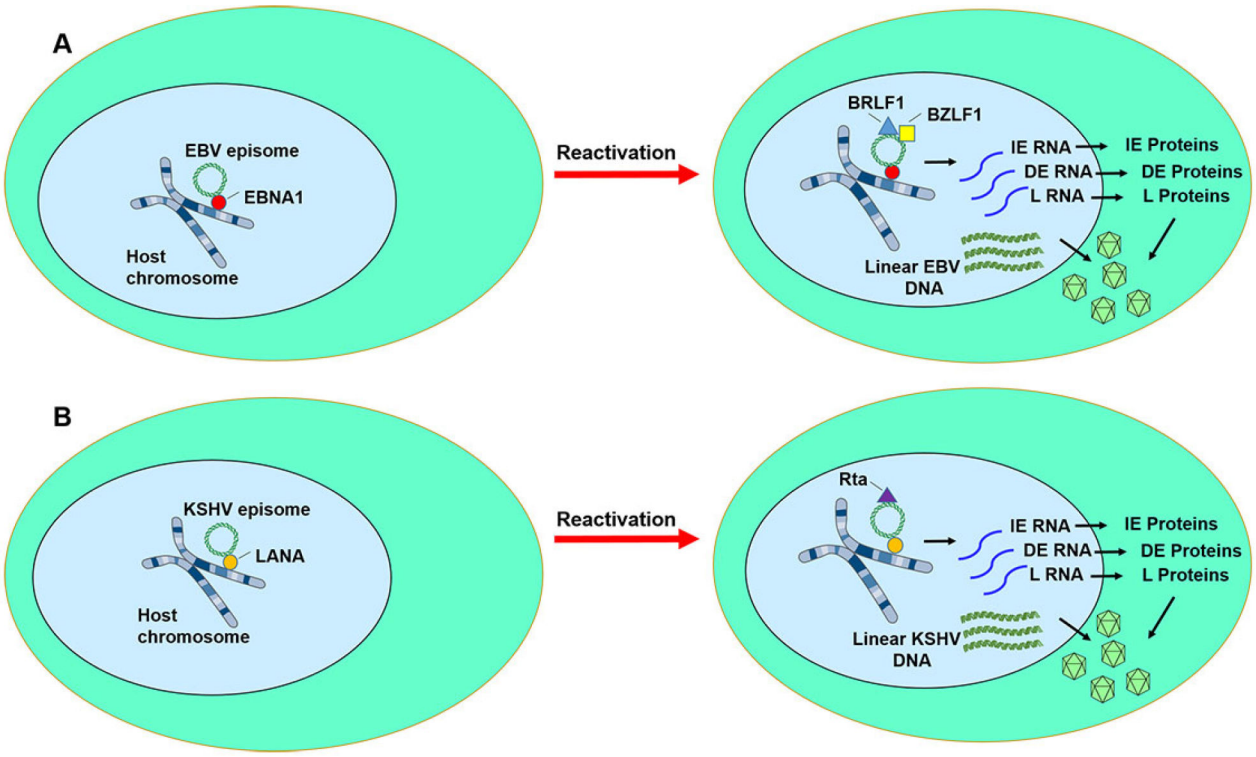

Figure 2.

Epstein-Barr virus (EBV) and Kaposi sarcoma-associated virus (KSHV) latency and reactivation. A) During EBV latent infection, very limited numbers of viral gene such as Epstein-Barr nuclear antigen-1 (EBNA1) and latent membrane proteins (LMP1 and LMP2) are expressed. EBNA1 (red circle) tethers the EBV episome (green ring) to the host chromosome. When reactivation is triggered, immediate early genes (e.g., BZLF1 and BRLF1) initiate lytic viral transcription, resulting in the orderly expression of immediate early (IE) genes, delayed early (DE) genes, and late (L) genes. Linear viral DNA molecules are replicated. Viral particles (blue pyramid structures) are produced and then released. B) During KSHV latent infection, very limited number of viral genes such as LANA (orange circle) are expressed. Latency-associated nuclear antigen (LANA) tethers the KSHV episome (green ring) to the host chromosome. When reactivation is triggered, the immediate early gene, RTA/ORF50 initiates lytic viral transcription, resulting in the orderly expression of immediate early (IE) genes, delayed early (DE) genes, and late (L) genes. Viral particles (blue pyramid structures) are produced and then released. Figure was created using artwork images from https://smart.servier.com/image-set-download/.

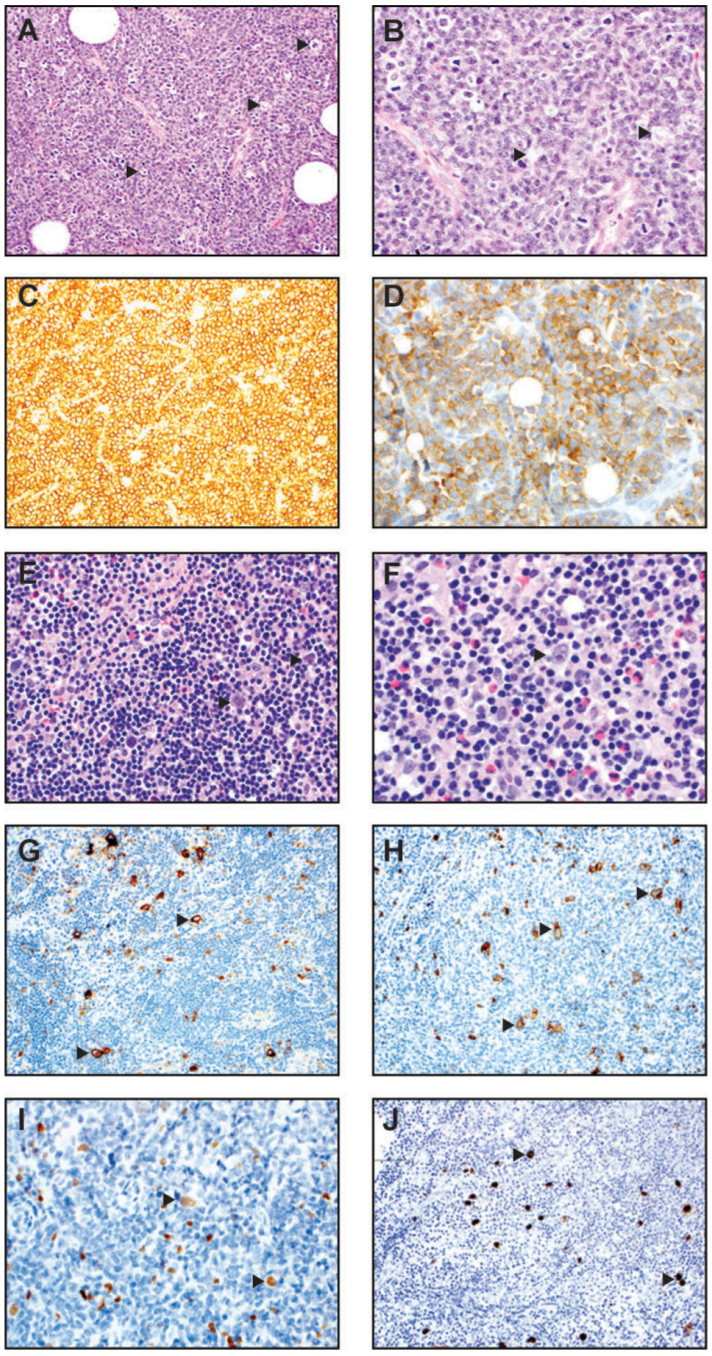

Figure 3.

Burkitt lymphoma (A-D) and classic Hodgkin lymphoma, mixed cellular type (E-J). (A) At medium power of H&E (200x), a characteristic starry-sky pattern is present. The “stars” (arrowheads) are represented by tingible-body macrophages and the “sky” is composed of neoplastic lymphoid cells. (B) At high magnification of H&E slide (400x), the neoplastic cells are intermediate-sized, with slightly irregular nuclear contours, few nucleoli, and basophilic cytoplasm. Arrowheads mark tingible-body macrophages. Many mitotic figures and apoptotic debris are also present. (C) The neoplastic cells are strongly positive for

the B cell marker CD20 (200x). (D) They are strongly positive for CD10 (400x) and BCL6 (not shown) consistent with a germinal center phenotype. (E) In this lymph node, the high-power magnification of H&E (400x) shows binucleate Reed-Sternberg (RS) cells (highlighted by arrowheads) and mononucleate Hodgkin (H) cells within a polymorphous background composed of small lymphocytes, histiocytes, eosinophils, and plasma cells. (F) A higher power magnification of H&E (600x) shows similar morphologic features, with an arrow pointing to a binucleate Reed-Sternberg H&E (600x). (G) Immunohistochemistry for CD30 (200x) highlights scattered RS and H cells (arrowheads). (H) Immunohistochemistry for CD15 (200x) highlights scattered RS and H cells (arrowheads). (I) The neoplastic RS and H cells (arrowheads) demonstrate variably weak positivity for PAX-5 immunostain. (J) The neoplastic RS and H cells (arrowheads) in this case are positive for EBV-encoded small RNA by *in situ* hybridization (400x).

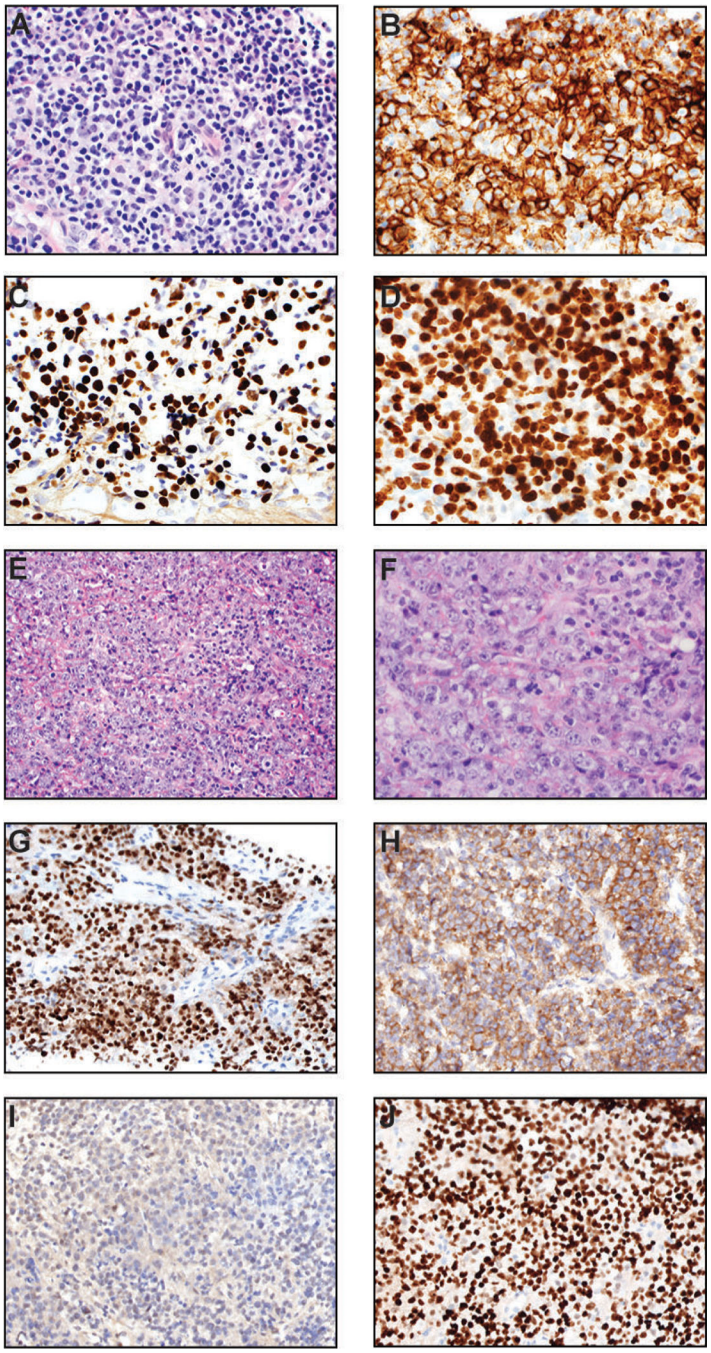

Figure 4.

EBV-positive diffuse large B cell lymphoma, not otherwise specified (NOS) (A-D) and plasmablastic lymphoma (E-J). (A) H&E section (400x) of this case shows variable sizes, but there is a significant number of large cells. (B) CD20 immunostain (400x) highlights diffuse proliferation of neoplastic cells. (C) These lymphomatous cells are positive for EBV-encoded small RNA (400x). (D) Ki-67 immunostain (400x) exhibits a very high proliferative index. (E) At this medium power of H&E (200x), the plasmablastic lymphoma shows a diffuse pattern with scattered tingible-body macrophages. (F) At this higher power

magnification of H&E (400x), the lymphomatous cells show pleomorphism with vesicular chromatin. Some nuclei contain single prominent nucleoli (immunoblastic morphology). Mitotic figures and karyorrhectic debris are frequently present. (G) *In situ* hybridization (ISH) for EBV-encoded small RNA (400x) shows positivity in essentially all lymphoma cells. (H) Kappa ISH (400x) in this case demonstrates that the tumor cells express the immunoglobulin kappa light chain. (I) Lambda ISH (400x) in this same case is negative in lymphoma cells, confirming kappa light chain restriction. (J) The PBL cells typically show diffuse and strong nuclear expression of MUM1/IRF-4 (400x). In this case, CD138 (syndecan-1) is also diffusely positive (not shown) to support plasmacytic differentiation.

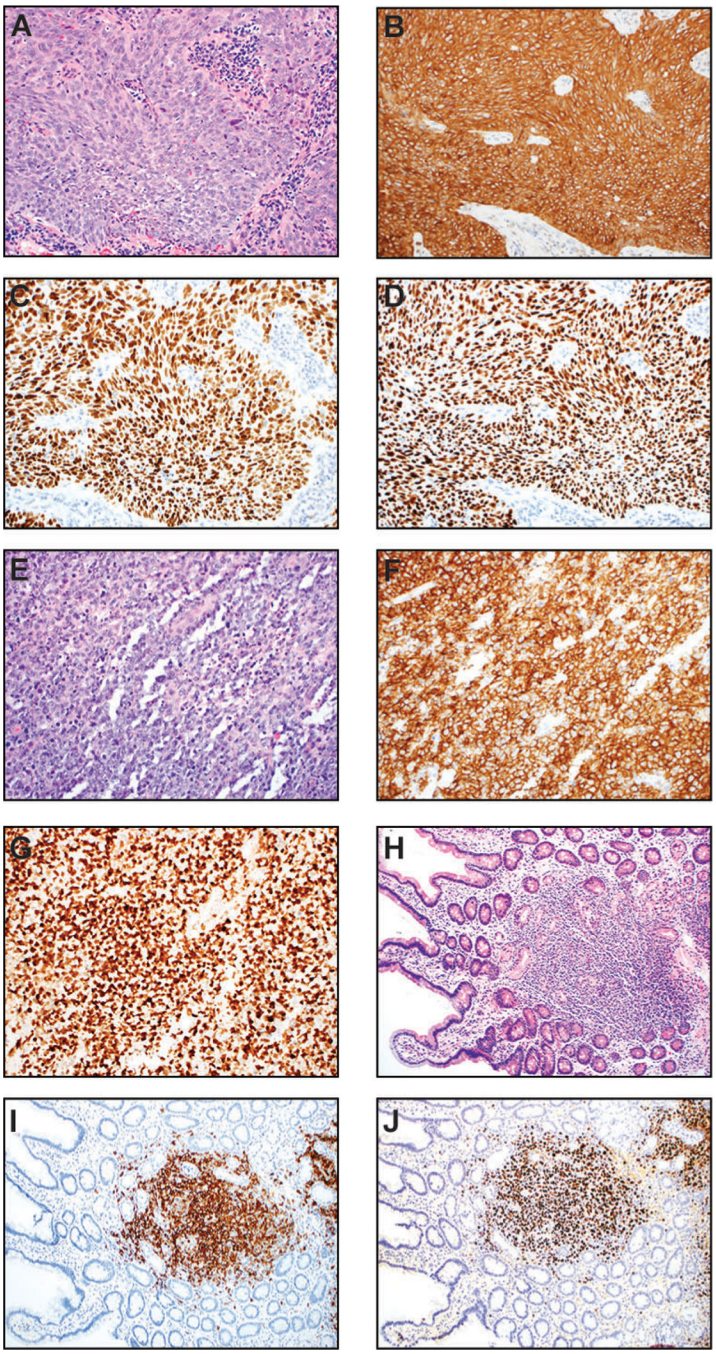

Figure 5.

Nasopharyngeal carcinoma (NPC) (A-D) and posttransplant lymphoproliferative disorder (PTLD) (E-J). (A) In this medium power H&E image (200x), the NPC grows in syncytial nests and show a spindled cell morphology. The neoplastic cells are large with oval nuclei, vesicular chromatin, and prominent nucleoli. (B) CK5/6 immunostain (200x) is diffusely and strongly positive in tumor cells, supporting squamous differentiation. (C) EBV-encoded small RNA (200x) is virtually positive in all tumor nuclei. (D) The tumor nuclei are also diffusely and strongly positive for p63, another squamous cell marker (200x). (E-G):

Monomorphic PTLD (diffuse large B-cell lymphoma type) in the central nervous system of a patient with prior renal transplant (15 years ago). (E) H&E (200x) shows a diffuse infiltrate of atypical large lymphoid cells with vesicular chromatin. Abundant apoptotic debris and mitotic figures are present. (F) CD20 immunostain (200x) confirms B-cell origin and large cell sizes. (G) Ki-67 (200x) immunohistochemistry highlights numerous neoplastic lymphoid cells with a very high proliferation index. (H-J) Duodenal polymorphic PTLD in a patient who had multiple stem cell transplants. (H) H&E section at a low power magnification (100x) shows mucosal involvement by a mixed hematolymphoid infiltrate. (I) CD20 (100x) demonstrates that the majority of cells are B-cells with variable sizes. (J) *In situ* hybridization for EBV-encoded small RNA (100x) highlights numerous EBV-positive lymphoid cells.

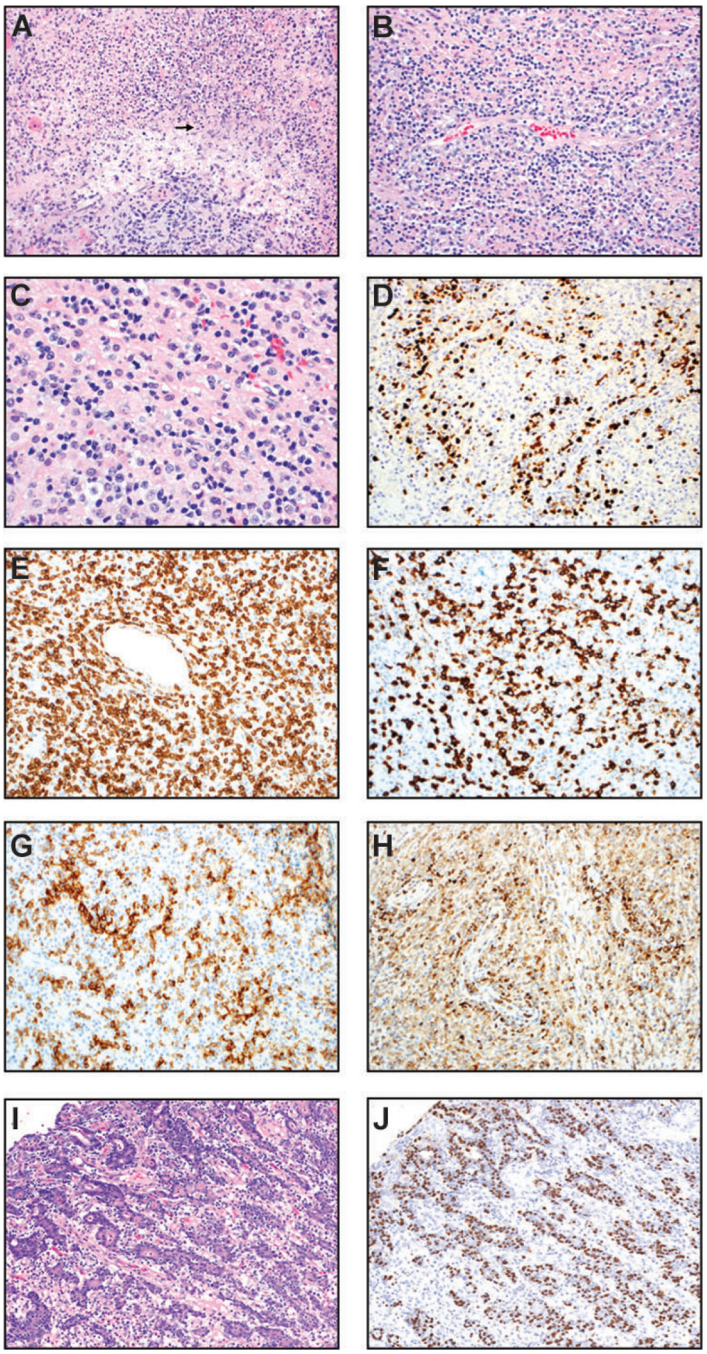

Figure 6.

Extranodal natural killer (NK)/T cell lymphoma, nasal type (A-H) and gastric carcinoma associated with EBV (I-J). (A & B) H&E sections (200x) show angiodestruction by invading lymphoma cells with associated necrosis and karyorrhectic debris (arrow in Panel A). (C) In this high-power H&E image (400x), most lymphoma cells are small to intermediate-sized with irregular nuclear contours/folds. Many cells possess moderate amounts of clear/vacuolated cytoplasm. (D) *In situ* hybridization for EBV-encoded RNA (200x) is positive in the nuclei of most lymphoma cells. (E) CD3 (200x) demonstrates that the majority of

the lymphoid infiltrate is T cells. (F) CD8 immunostain is positive in the neoplastic T cells with angiocentric pattern (200x). (G) CD56 immunostain highlights the angiocentric lymphoma cells (200x). (H) TIA-1 immunostain highlights the angiocentric lymphoma cells. (I-J) Gastric carcinoma associated with EBV: Gastric carcinoma with lymphoid stroma. (I) H&E (200x) slide shows epithelioid tumor cells in fused glands and cords. There are intraepithelial lymphocytes as well as mature lymphocytes scattered in the background. (J) *In situ* hybridization for EBV-encoded RNA (200x) is positive in the nuclei of the neoplastic epithelial cells but not the background lymphocytes.

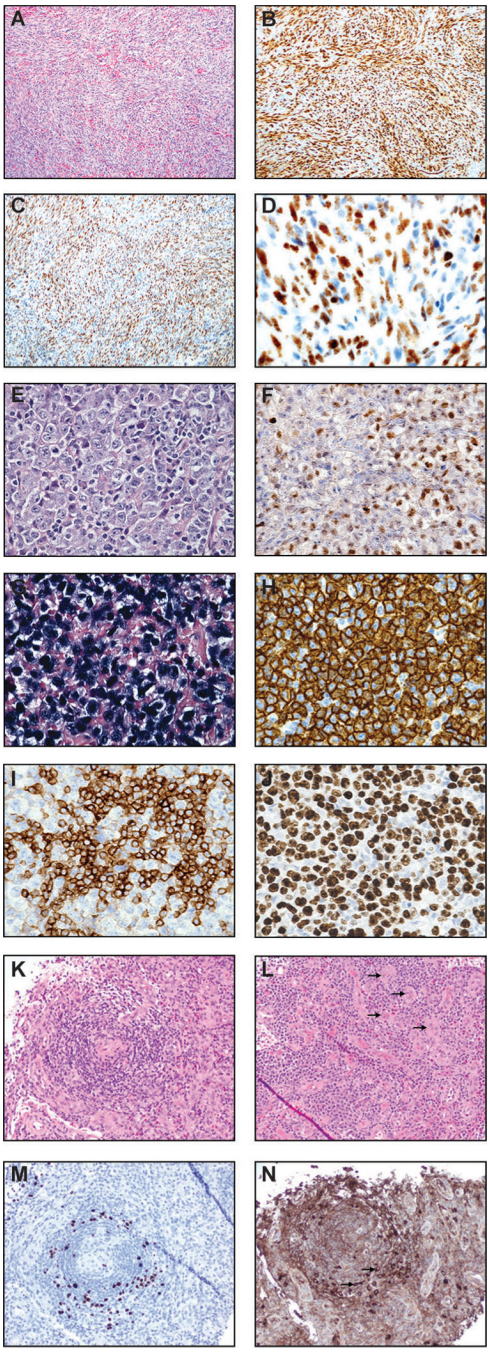

Figure 7.

Kaposi sarcoma (A-D), primary effusion lymphoma (PEL) (E-J), and multicentric Castleman disease (K-N). (A) H&E image (100x) of a lymph node involved by Kaposi sarcoma shows intersecting fascicles of spindled cells. There are intervening slit-like/sieve-like spaces with entrapped red blood cells. (B) ERG immunostain (100x) is positive in essentially all spindled cells. Other vascular markers such as CD31 and CD34 are also positive in KS (not shown). (C) KSHV LANA immunostain (100x) is positive in virtually all nuclei of Kaposi sarcoma cells. (D) KSHV LANA immunostain at a high

power (400x) demonstrates the classic punctate/speckled staining of KS nuclei. Primary effusion lymphoma (PEL) (E-J). (E) H&E image at high power field (600x) displays large and pleomorphic PEL cells with anaplastic nuclei, variably prominent nucleoli, and abundant cytoplasm. There is plasmablastic morphology. Mitotic figures and mummified cells are easily identified. (F) KSHV LANA stain (600x) shows positive staining in PEL nuclei, a key to the diagnosis. (G) *In situ* hybridization stain for EBV-encoded small RNA (600x) highlights neoplastic cells in this PEL case. (H) CD30 immunostain (600x) shows diffuse and strong membranous and cytoplasmic staining of PEL cells. (I) MUM1/IRF-4 stain (600x) demonstrates plasmacytic differentiation. (J) Ki-67 immunostain (600x) demonstrates a high proliferation index. Multicentric Castleman disease (K-N). (K) H&E image (200x) shows a regressed germinal center concentrically involved ("onion skinning" pattern) by numerous lymphoid cells and plasma cells/plasmablasts. (L) H&E image (200x) demonstrates numerous plasma cells in clusters and increased vessels (arrows). (M) KSHV LANA stain (200x) highlights plasmablasts. (N) Lambda immunostain (200x) highlights monotypic plasmablasts.

Table 1.

EBV cancers and their respective latent states and gene products.

	Healthy individuals	GC or EN NK/T-cell lymphoma	BL	CHL	NPC	EBV+ LBCL or PTLD
EBNA1		+	+	+	+	+
LMP1				+	+	+
LMP2			+	+	+	+
EBER	+	+	+	+	+	+
BART miRNA	+	+	+		+	
EBNA2						+
EBNA3A/3B/3C						+
Latency state	0	I	I	II	I/II	III

Abbreviations: NPC: nasopharyngeal carcinoma; BL: Burkitt lymphoma; CHL: classic Hodgkin lymphoma; EBV: Epstein Barr virus; EN: extranodal; GC: gastric carcinoma; LBCL: Large B-cell lymphoma; NK: natural killer; NPC: nasopharyngeal carcinoma; PTLD: posttransplant lymphoproliferative disorder

Table 2.

Example of HHV-8/KSHV respective gene/protein expression in its associated human cancers [1–3].

	KS	PEL	MCD
LANA (ORF73)	+	+	+
K8	+	+	+
K10	−/+	+	+
K11	+	+	
K15	+		
ORF59/PF8	+		+
ORF65	+		
K2		+	+
vIL6		+	+
K12/kaposin	+	+	+
vFLIP	+	+	+
vCyclin	+	+	+
K9/vIRF-1			+
K10.5/LANA2		+	+
K10	−/+	+	+

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