Chapter 12
Kaposi's Sarcoma-Associated Herpesvirus: Pathogenesis and Host Immune Response

Louise Giffin, Penny Anders, and Blossom Damania

Introduction

Kaposi's sarcoma-associated herpesvirus (KSHV) (also known as human herpesvirus 8 or HHV-8) was first discovered by Drs. Yuan Chang and Patrick Moore in 1994 in Kaposi sarcoma lesions from HIV-infected individuals [1]. Since its discovery, KSHV has also been linked to two lymphoproliferative diseases, primary effusion lymphoma (PEL) and multicentric Castleman's disease (MCD) [2, 3]. More recently, KSHV has been found to be associated with an inflammatory condition called KSHV-inflammatory cytokine syndrome (KICS) [4, 5].

Kaposi sarcoma (KS) lesions are highly angiogenic and the skin lesions are visibly red due to the high degree of vascularization. The vessels in KS lesions are prone to fluid leakage and extravasation of red blood cells. KS progresses through different stages that include patch, plaque, and nodular. The lesions contain inflammatory cells and slit-like neovascular spaces. The elongated, spindle-shaped cells in these lesions are thought to be endothelial in origin. These cells are all infected with KSHV and are thought to be the drivers of KS pathogenesis. Spindle cells display many markers of the endothelial cell lineage, including factor XIII, CD31, CD34, and CD36 [6]. Interestingly, KSHV infection of vascular and lymphatic endothelial cells reprograms their transcriptional profile towards a lymphatic or vascular lineage, respectively, thus giving rise to pleiotropic marker expression in these spindle cells [7–10].

Kaposi sarcoma is named after the Hungarian dermatologist, Moritz Kaposi, who identified these lesions as "Idiopathisches multiples Pigmentsarkom der Haut," or idiopathic multiple pigmented sarcoma of the skin [11]. The KS lesions seen by

L. Giffin • P. Anders • B. Damania, Ph.D. (✉)
Department of Microbiology and Immunology, Lineberger Cancer Center, CB#7295, University of North Carolina at Chapel Hill, Room 31-303, Chapel Hill, NC 27599, USA
e-mail: blossom_damania@med.unc.edu

S.D. Hudnall (ed.), *Viruses and Human Cancer*, DOI 10.1007/978-1-4939-0870-7_12,

Kaposi were found on elderly Mediterranean men and are known as "classic KS." KS is common in certain geographical regions such as in Mediterranean countries and parts of Africa [12, 13]. Before the advent of HIV, KS was rare; however, following the AIDS epidemic, KS was identified as one of the most common AIDS-defining cancers. Currently, there are thought to be four classes of KS:

1. Classic KS
2. Endemic or African KS
3. Iatrogenic KS associated with immunosuppressive therapies in transplant patients
4. Epidemic or AIDS-related KS

In contrast, PEL is an expansion of B cells in the pericardial, pleural, and peritoneal spaces, although PEL can also occur in solid organs. Unlike KS, the KSHV-infected B cells in PEL have a clonal origin [14, 15]. Each PEL cell contains many copies of the KSHV episome. Another B cell disorder linked to KSHV infection is the plasmablastic variant of MCD [16]. In AIDS patients, MCD can manifest as an aggressive malignancy that is almost always associated with KSHV infection [3]. The most newly recognized disease associated with KSHV is KICS. KICS is similar to KSHV-MCD in that KICS patients have elevated viral interleukin-6 (vIL-6), human IL-6, and IL-10 levels and high KSHV viral titer compared to KS patients. Unlike KSHV-MCD, KICS patients do not suffer from proliferating plasmacytoid B lymphocytes in the lymph node [4, 5].

Virion Structure and Viral Genome

KSHV virions comprise an electron-dense nucleocapsid that is surrounded by a lipid bilayer envelope. A proteinaceous layer called the tegument, which exists between the capsid and the envelope, contains multiple proteins and viral RNA transcripts [17–19]. The virion contains multiple glycoproteins including gB, gH, gM, gL, gN, ORF68, and K8.1 [17]. KSHV has an icosahedral capsid that is symmetric ($T=16$) with 20 triangular faces [20–22]. The capsid is made up of six proteins, including the major capsid protein (MCP, ORF25), a heterotrimer triplex protein containing one copy of ORF62 and two copies of ORF26, the small capsid protein (ORF65), scaffold protein (ORF17.5), and protease (ORF17). The capsomers comprise hexamers and pentamers of MCP. Each capsid contains 150 hexons and 12 pentons and these are interconnected by 320 copies of the triplex heterotrimer [21, 23–25]. The viral genomic DNA is linear [26] and is located inside the capsid.

Sequencing of the KSHV genome revealed its similarity to other members of the gammaherpesvirus family. The gammaherpesviruses are divided into two groups: the γ1 or lymphocryptoviruses, which includes Epstein–Barr virus (EBV), and the γ2 or rhadinoviruses, which includes KSHV [27, 28]. The genome is 165–170 kb

long with 140 kb of unique coding sequence flanked on either side by repetitive terminal repeat sequences [27]. The KSHV ORFs are numbered consecutively from left (ORF 1) to right (ORF 75). ORFs unique to KSHV are denoted by a "K" designation [28, 29]. The KSHV genome also encodes many noncoding RNAs, including microRNAs [29–32] and other noncoding RNAs, e.g., PAN [33–36].

Viral Entry

KSHV encodes three glycoproteins, gB, gH, and gL, which can mediate membrane fusion [37]. KSHV is thought to bind to the cell via a number of different cellular receptor proteins. KSHV gB, gH, ORF4, and gpK8.1A bind heparin sulfate [38–42]. It is likely that heparin sulfate binding allows for a concentration of virions on the cell membrane, which may help to increase the concentration of viruses that can interact with cell surface receptors. KSHV gB contains an integrin-binding RGD (Arg-Gly-Asp) motif that enables virus entry [38, 39, 43] by interacting with αVβ3 and αVβ5 integrins on cells [44]. In activated B cells, dendritic cells (DCs), and macrophages, dendritic cell-specific intercellular adhesion molecule 3 (ICAM-3)-grabbing non-integrin (DC-SIGN; CD209) can also bind KSHV [45, 46]. Collectively, heparan sulfate, integrins, and DC-SIGN are all thought to interact with KSHV and contribute to binding of the virus to the cell. xCT, a 12-transmembrane glutamate/cysteine exchange transporter protein, can also serve as a receptor [47]. xCT is part of the CD98 (4F2 antigen) complex that contains a glycosylated heavy chain and several 45-kDa light chains. Ephrin receptor tyrosine kinase A2 (EphA2) has also been identified as a cellular receptor. Binding of EphA2 to the viral glycoprotein dimeric complex gH-gL results in the phosphorylation and endocytosis of EphA2 in epithelial and endothelial cells [48]. EphA2 has also been shown to be a master regulator of macropinocytosis in human dermal microvascular endothelial cells by facilitating the recruitment of various signaling molecules to the entry site and by regulating the activation of KSHV-induced signaling molecules [49]. KSHV primarily enters cells by clathrin-mediated endocytosis [50–53] (Fig. 12.1), although it can also enter through macropinocytosis [52]. Virus binding to the cell initiates a host cell signaling cascade that allows the virus to modulate the cellular microenvironment to its advantage. Binding of KSHV to cell surface receptors such as integrins stimulates the phosphorylation and activation of focal adhesion kinase (FAK), which in turn activates other proteins including PI3K, Src, Rho GTPases, and Diaphanous 2 [40, 43, 51, 54–63]. Activation of PI3K and Rho GTPase causes rearrangement of the cytoskeleton and formation of lamellipodia (Rac), stress fibers (RhoA), and filopodia (Cdc42). Priming of the microtubules enables the delivery of viral capsids to the nuclear membrane [57, 61]. KSHV also activates the mitogen-activated protein kinase (MAPK) pathway, specifically ERK1/2, as well as the NFκB pathway; both of these pathways help initiate viral gene expression in infected cells [40, 56, 58, 62, 64].

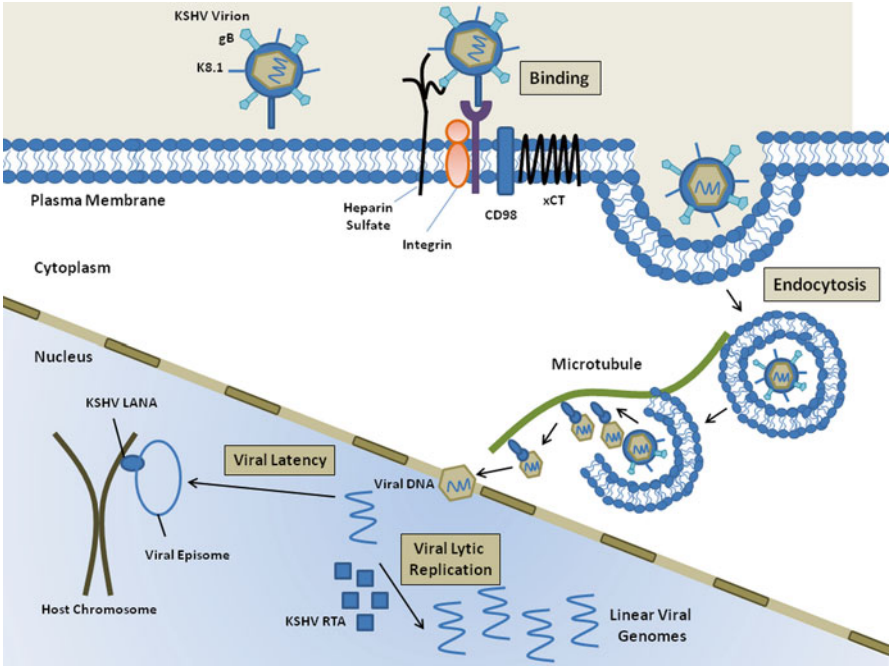

Fig. 12.1 Viral entry. The various stages of KSHV entry are depicted. The virion binds various cellular receptors and primarily enters the cell by clathrin-mediated endocytosis. Signaling initiated by virion binding modulates the cytoskeleton to facilitate delivery of the virion to the nucleus. After the KSHV genome enters the nucleus, the decision to enter the latent or lytic phase of the viral lifecycle occurs

Cellular Targets of Infection and the Viral Lifecycle

In vitro, KSHV can infect a wide range of cell types including fibroblasts, keratinocytes, B lymphocytes, monocytes, plasmacytoid dendritic cells (pDCs), endothelial cells, and epithelial cells [45–47, 50, 64–75]. However, in vivo, KSHV is known to infect B cells and endothelial cells [76–78], epithelial cells [79–81], and monocytes [82].

KSHV has two phases to its lifecycle: latency and viral lytic replication (Fig. 12.2). During latency, the viral genome exists as a circular episome that is tethered to the host chromosomes via a viral protein named latency-associated nuclear antigen (LANA). Viral gene expression is restricted and only a small number of viral genes are expressed. In contrast, during lytic replication nearly all viral genes are expressed, which allows for amplification of viral genomes and the subsequent assembly, egress, and dissemination of progeny virions. The lytic switch protein, ORF50 or Replication and Transcription Activator (RTA), is the master switch that controls KSHV reactivation [83, 84]. In cell culture, chemicals such as sodium butyrate, histone deacetylase

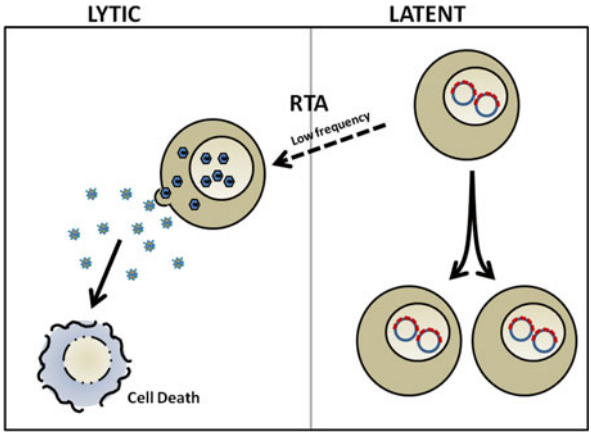

Fig. 12.2 Latency and reactivation. Following infection, KSHV typically establishes latency in the host cell. RTA is the virally encoded lytic switch protein that induces sporadic bouts of lytic reactivation and viral replication

inhibitors, and phorbol esters reactivate the virus [85]. Other triggers include cytokines such as oncostatin M, interferon-γ, and hepatocyte growth factor. Hypoxia, or oxygen deprivation, as well as terminal differentiation of B cells induced by X-box-binding protein 1 (XBP-1) expression can also reactivate KSHV [86–89]. Finally, activation of toll-like receptors (TLRs) 7 and 8 by microbes can induce KSHV reactivation from latently infected cells [90]. Host cellular factors such as the tousled-like kinases (TLKs) can also control KSHV reactivation from latency. Depletion of TLKs in KSHV latently infected cells results in viral reactivation [91]. Chromatin organizing factors such as cohesins have a regulatory role in maintaining KSHV latency by binding and repressing transcription of the immediate early gene cluster. Depletion of cohesions in PEL cells results in RTA expression and viral replication [92]. Spontaneous reactivation from latency occurs both in cell culture and in vivo and the primary site of lytic virus replication in humans is the oropharynx [73, 93–96]. Clinical data demonstrates that shedding of virus during periodic bouts of lytic reactivation is intermittent and usually asymptomatic [94, 97].

Viral Latency

The KSHV latent genes are encoded by a major latency locus that is transcribed in all latent KSHV-infected cells (Fig. 12.3). This locus encodes LANA, viral cyclin (v-cyclin), v-FLICE-inhibitory protein (v-FLIP), and the kaposins (K12). The LANA, v-cyclin and v-FLIP genes are under the control of the LANA promoter [98–100]. The three kaposin transcripts (A, B, C) are driven by the kaposin promoter, which can also generate a bicistronic transcript for v-cyclin and v-FLIP [101]. Twelve virally encoded pre-miRNAs are also transcribed using this promoter [30–32, 102, 103]. All of these latent genes are expressed in KS and PEL cells [104, 105]. Additionally, PEL cells express v-IRF3 (also called LANA-2) during latency [106].

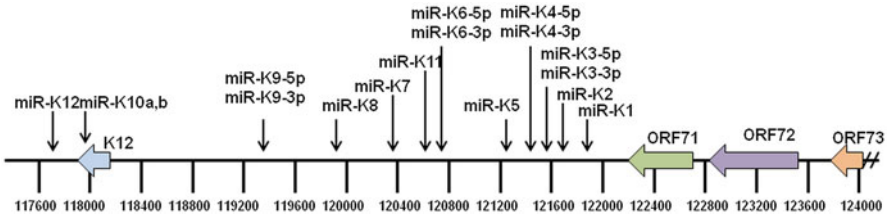

Fig. 12.3 The latency locus of KSHV. The latent genes include Orf73/LANA, Orf72/vCyclin, Orf71/vFLIP, and Kaposin/K12. The KSHV latency locus also expresses a number of viral pre-microRNAs that are processed into 18 mature microRNAs

LANA

Latency-associated nuclear antigen (LANA), the major latency protein, plays a critical role in latent viral replication. LANA simultaneously binds the viral episome (via the latent origin of replication in the terminal repeats) and cellular histones H1, H2A, and H2B [107–114], thus tethering the episome to host chromosomes. Latent viral DNA replication is performed by the host's DNA polymerase. Therefore, during cell division, viral genomic DNA undergoes replication and segregation concurrently with host chromosomes, allowing distribution of viral genomes to daughter cells [113–115].

Aside from its function in replication and maintenance of the KSHV latent genome, LANA promotes tumorigensis by altering cellular pathways involved in cell proliferation and survival. LANA extends the life span of endothelial cells [116]. LANA transgenic mice display splenic follicular hyperplasia and enhanced germinal center formation [117], B cell lymphomas, and an increased response to antigen stimulation [118]. LANA binds p53, and cells that express LANA have reduced activation of p53-dependent reporter genes [119]. However, most PEL respond to p53-activating DNA damaging agents [120]. LANA also binds the tumor suppressor Rb resulting in functional inactivation of Rb and increased E2F-dependent reporter gene activation [121].

LANA also interacts with GSK-3β, which phosphorylates and inactivates β-catenin through ubiquitin-mediated proteosomal degradation [122]. LANA's binding to GSK-3β induces its relocation to the nucleus, which allows β-catenin to accumulate in the cytoplasm. This allows for the transcription factor LEF to move into the nucleus to activate expression of cyclin D and c-myc [122]. LANA can also increase c-Myc protein stability [123, 124]. Moreover, LANA contributes to tumorigenesis by inducing chromosome instability. LANA interacts with the spindle checkpoint protein, Bub1, and dysregulates its activity leading to irregular chromosome replication [125].

As a nuclear protein, LANA has transcriptional effects on the Rb/E2F pathway [126–128]. Although LANA can activate transcription of certain genes [126–128], LANA is predominantly a repressor of transcription [111, 129, 130]. LANA interacts

with RBP-Jκ (also called CBF-1 or CSL) and is targeted to RBP-Jκ sites in the ORF50 promoter to repress RTA transcription [131]. LANA also associates with the cellular transcription repressors Krüppel-associated box domain-associated protein-1 (KAP1) and Sin3A to repress the lytic promoter RTA during primary KSHV infection, thereby promoting the establishment of latency [132, 133].

vCyclin

vCyclin shows homology to cellular cyclin D. vCyclin binds and activates cdk6 in a similar fashion as its cellular homolog [134]. vCyclin can also induce phosphorylation of histone H1, p27, nucleophosmin (NPM), Id-2, and cdc25a [135–137]. vCyclin promotes S-phase entry and can overcome Rb-mediated cell cycle arrest mediated by cdk inhibitors [138]. Phosphorylation of p27 by vCyclin-cdk6 targets p27 for degradation thereby inhibiting the regulation of cdk6 by p27 [139, 140]. vCyclin also opposes senescence and G1-arrest induced by vFLIP (see section on vFLIP)-activated NFκB by resisting cdk inhibitors and by targeting p27 for degradation [141]. Interestingly, vCyclin can also bind cdk9 resulting in increased phosphorylation of p53 and subsequent cell cycle arrest [142]. vCyclin transgenic mice develop lymphomas only in animals deficient for p53 [143, 144]. vCyclin transgenic mice also display severe lymphatic dysfunction and develop chylous ascites [145]. Therefore, vCyclin is not sufficient to induce tumorigenesis, but it contributes to cellular transformation by promoting cell cycle progression and proliferation when cells are in a contact-inhibited state [146].

vFLIP

KSHV vFLIP or K13 is the viral homolog of cellular FLIP (FLICE [protein FADD-like interleukin-1 beta-converting enzyme, now called caspase-8] inhibitory protein). vFLIP contains two death effector domains (DEDs) that allows for homotypic protein–protein interactions with other DED-containing proteins. Overall, vFLIP has been shown to inhibit Fas-dependent apoptosis [147–149], with the exception of one report [150]. vFLIP upregulates the NFκB signaling pathway [151–155] and can bind NEMO (also called IKKγ) in PEL cells [156–158]. This complex activates IKK, resulting in IκB phosphorylation and the release of active p65-p50 NFκB heterodimers [159]. Binding of vFLIP to the adaptor NEMO and activation of NFκB are essential for protecting cells against death receptor-induced cell death [160]. Moreover, vFLIP enhances interferon regulatory factor 4 (IRF4)-mediated gene transcription [161] and induces the expression of IL-1β, IL-18, and caspase-1 transcripts via NFκB [162]. Expression of vFLIP protects B cells from B cell receptor-induced apoptosis by NFκB activation [163]. Transgenic vFLIP mice displayed an increased incidence of lymphoma and enhanced responses to mitogenic stimuli

[150, 164]. A separate line of vFLIP transgenic mice displayed B cell-derived tumors and lymphadenopathy with an increased number of lambda light chain-expressing plasmablasts, similar to MCD [149].

Kaposin/K12

The kaposin locus encodes three proteins: kaposins A, B, and C [165]. Kaposin A is a small transmembrane protein that can transform cells in vitro [166, 167]. Kaposin B activates the p38 MAPK signaling pathway by direct interaction with the kinase MK2, a p38 substrate [168]. This results in the stabilization of cytokine and growth factor mRNAs [168]. Kaposin B also induces phosphorylation of STAT3 and MK2-mediated phosphorylation of TRIM28 thus relieving STAT3 repression from TRIM28 and enhancing inflammation [169].

Viral miRNAs

The KSHV pre-miRNAs produce 18 mature miRNAs [170]. Both host and viral mRNAs are targeted by the KSHV miRNAs. KSHV miRK9-3p (also called miRK9*) targets the expression of the viral RTA protein [171] while several viral miRNAs including miR-K12-1, miR-K12-3-3p, miR-K12-6-3p, and miR-K12-11 target thrombospondin, an anti-angiogenic protein [172]. One KSHV miRNA, miRK11, shares seed sequence identity with a lymphoid-specific host miRNA (miR155) that modulates B cell differentiation [173–175]. Deletion of a 14-miRNA cluster from the viral genome increased viral lytic replication due to lowered NFκB activity [176]. Thus, the KSHV miRNAs modulate KSHV viral latency and lytic replication. KSHV miRNAs also regulate cell transformation and tumorigenesis by preferentially targeting pathways related to cancer including the NFκB pathway. KSHV mIR-K1 targets and reduces IκBα levels thereby facilitating NFκB activation, cell growth, and survival. Several KSHV miRNAs are implicated in promoting cell growth and survival by modulating levels of various host proteins. Moreover, some KSHV miRNAs regulate the levels of cellular proteins involved in the immune response and angiogenesis [177–179].

Viral Lytic Cycle

Like other herpesviruses, the lytic program of KSHV also displays a temporal order of gene expression: immediate early, delayed early, and late genes.

The RTA protein encoded by KSHV ORF50 is the key lytic switch protein that controls reactivation from latency and initiates lytic replication. Ectopic expression

of RTA alone can induce reactivation from latency [83, 180, 181] and deletion or inactivation of RTA prevents reactivation from latency [84, 182]. ORF50 is an immediate-early protein as it is transcribed in the presence of cycloheximide, meaning no other viral protein synthesis is required for ORF50 expression [83, 183, 184]. ORF50 is the first transcript to be made during reactivation following chemical induction of PEL with TPA [181, 185]. This is because the ORF50 promoter is induced by TPA and lytic induction is associated with demethylation of the ORF50 promoter [186, 187]. ORF50, K8, and K8.1 genes are all part of a polycistronic transcript.

KSHV RTA has an amino-terminal DNA-binding domain (DBD) and a carboxy-terminal activation domain. ORF50 can bind to and activate many different KSHV viral promoters as well as the two origins of lytic replication, OriLyt-L and OriLyt-R [188]. The RTA/ORF50-binding sites are called RTA-response elements (RREs), although many of the RREs share limited sequence homology [189–199]. Although ORF50 can directly bind DNA to transcriptionally activate promoters, it can also interact with other cellular transcription factors such as RBP-Jκ [192]. RBP-Jκ recognition sites are found in several ORF50-responsive gene promoters [189, 192, 196, 199–201]. ORF50 can also bind the transcription factors C/EBPα [190, 202], Oct-1 [203], and STAT-3 [204]. Additionally, ORF50 can interact with factors involved in chromatin modification such as CBP and histone deacetylase 1 [205], the chromatin remodeling complex SWI/SNF, and the TRAP/Mediator complex, which enables interaction of RNA pol II with many transcription factors [206].

The spliced isoform of plasma cell transcription factor X box-binding protein 1 (XBP-1s) can also govern the switch from latency to lytic replication [88, 89]. XBP-1s is not present in PEL, but the induction of hypoxia or endoplasmic reticulum stress gives rise to XBP-1s and subsequent induction of the lytic cycle [89, 207]. In addition to ORF50, ORFs K8, ORF45, and K4.2 are also classified as immediate early genes, although some reports classify them as delayed early (DE) genes.

DE genes encode transcripts that are sensitive to cycloheximide (since their expression depends on activation of their promoters by IE proteins) but resistant to viral DNA synthesis inhibitors. DE proteins include the viral DNA polymerase, thymidine kinase, ribonucleotide reductase, ssDNA-binding protein, and polymerase processivity factor, which prepare the infected cell for the onset of viral DNA replication. Several other DE proteins function in nuclear-cytoplasmic transport of viral RNAs (ORF57), modulation of signal transduction (K1, K15, and vGPCR), and immune evasion (K3/MIR1 and K5/MIR2).

The delayed early lytic phase is followed by viral DNA replication. The core replication machinery is directed to the replication origins on the viral genome called oriLyts. The KSHV genome contains two oriLyt regions: the left-hand origin (oriLyt L) which lies between ORFs K4.2 and K5, and the right-hand element (oriLyt R) which lies between ORFs K12 and 71 [208, 209]. Viral genome replication is thought to occur in a rolling circle mechanism and linear genomes are produced and packaged into nascent capsids. The viral replication machinery comprise the KSHV viral DNA polymerase, helicase, polymerase processivity factor, primase,

primase-associated factor, and single strand-binding protein [210]. Following DNA replication, late gene expression ensues. Most late genes encode structural proteins such as capsid proteins and envelope proteins [99, 104, 211, 212].

Host Response to KSHV Infection and the Viral Counter Response

An innate immune response occurs following KSHV infection due to the detection of KSHV by various host cellular proteins including TLRs, IFI-16, and RIG-I like receptors. TLRs are the first line of defense against infecting microbes. TLRs detect pathogen-associated molecular patterns (PAMPs) present on the invading microbe and initiate signaling cascades leading to the activation of type I interferon (IFN) and NFκB and the production of proinflammatory cytokines [213]. TLRs can be expressed endosomally or on the cell surface. KSHV activates TLR3 during infection of primary human monocytes leading to the upregulation of TLR3 expression and its downstream mediators, including IFN-β1 and CXCL10 [75]. In human pDCs, which are the body's chief IFN-producing cells, viral infection activates TLR9, a DNA sensor [65]. KSHV is also sensed by another innate immune protein, the interferon gamma-inducible factor IFI-16, and IFI-16 colocalizes with the KSHV genome in the nucleus [214] and forms an inflammasome resulting in the production of IL-1β during primary and latent infection [162, 214]. The double stranded RNA sensor retinoic acid-inducible gene 1 (RIG-I) and its adaptor mitochondrial antiviral signaling protein (MAVS) also sense KSHV infection. Primary infected KSHV cells that have been depleted of RIG-I and MAVS have increased KSHV and reduced IFN-β transcription [215].

To counter the host-mediated immune response, KSHV encodes many gene products that thwart various arms of the host immune response. Several KSHV proteins are able to ablate the activation and function of type I IFNs produced in response to microbial infection. Activation of the innate immune response leads to the activation of cellular interferon regulatory factors (IRFs), e.g., IRF3 and IRF7, type I interferon (IFNα and IFNβ), and inflammatory cytokines. IFNα/β secreted from the infected cell can bind to IFNα and IFNβ receptors expressed on neighboring cells. IFN receptor activation induces signaling that stimulates transcription of many different IFN-sensitive genes (ISGs), and the cellular IRFs themselves.

The KSHV genome encodes four homologs of cellular IRFs. vIRF-1, -2, -3, and -4 were named based on their order of discovery. vIRF-3 is latently expressed but the other vIRFs (vIRF-1, -2, and -4) are mainly expressed during the lytic cycle. Although primarily a lytic gene, vIRF-1 can also be transcribed in latently infected KS cells [216, 217], vIRF-1 is transcribed in latently infected KS cells [105, 195]. vIRF-1, -2, and -3 cannot bind IRF-binding motifs in type I IFN and ISG promoters since they do not contain the DBDs of cellular IRFs (Fig. 12.4). vIRF-1 inhibits IFN activation in response to Sendai virus infection [216, 218] and dimerizes with cellular IRF1 and IRF3 to prevent their activation of IFN promoters. vIRF-1 can bind and sequester the

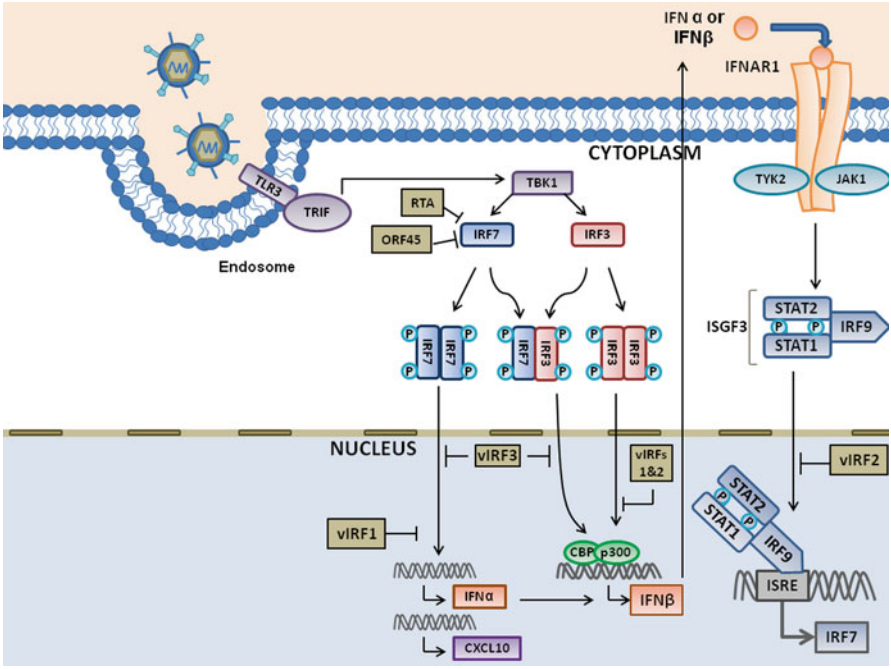

Fig. 12.4 The KSHV vIRFs. KSHV encodes four vIRFs that share varying amounts of homology with cellular IRFs. One function of the vIRFs is to block cellular IRF function and interferon activation that is initiated by the host cell's immune response to the virus

coactivator, CBP/p300, away from cellular IRFs, thereby inhibiting CBP/p300 histone acetyltransferase activity on IRF-driven promoters [217, 219, 220]. vIRF-2 inhibits cellular IRF1- and IRF3-mediated transcription [217, 221], IFNβ promoter activity [222], ISG56 activation [221], and ISRE transactivation [221]. Similar to vIRF-1 and vIRF-2, vIRF-3 can inhibit transactivation of the IFN-α4 and IFN-α6 promoter [223, 224]. vIRF-3 also inhibits IFNγ-mediated activation of the GAS promoter and CIITA promoters PIV and PII [225]. Downregulation of the CIITA promoters results in reduced major histocompatibility complex class II (MHC II) expression [226] and a hampered adaptive immune response.

Two other KSHV proteins that are not IRF homologs can also thwart cellular IRF signaling. ORF50 induces IRF7 degradation and ORF45 can bind IRF7 and prevent its phosphorylation and nuclear translocation [227, 228]. An ORF45-deleted virus was less able to replicate compared to wild-type virus [229, 230].

Two viral proteins, ORFs K3 and K5, inhibit presentation of MHC-I [231]. K3 and K5 encode for *m*odulators of *i*mmune *r*ecognition (MIR1 and MIR2, respectively). K5/MIR2 downregulates only HLA-A and HLA-B, while K3/MIR1 downregulates all four HLA allotypes (HLA-A, -B, -C, -E) [232, 233]. The KSHV MIR proteins functionally resemble the cellular MARCH protein family. This is a family of ubiquitin ligases that ubiquitinate cellular glycoproteins and target them for

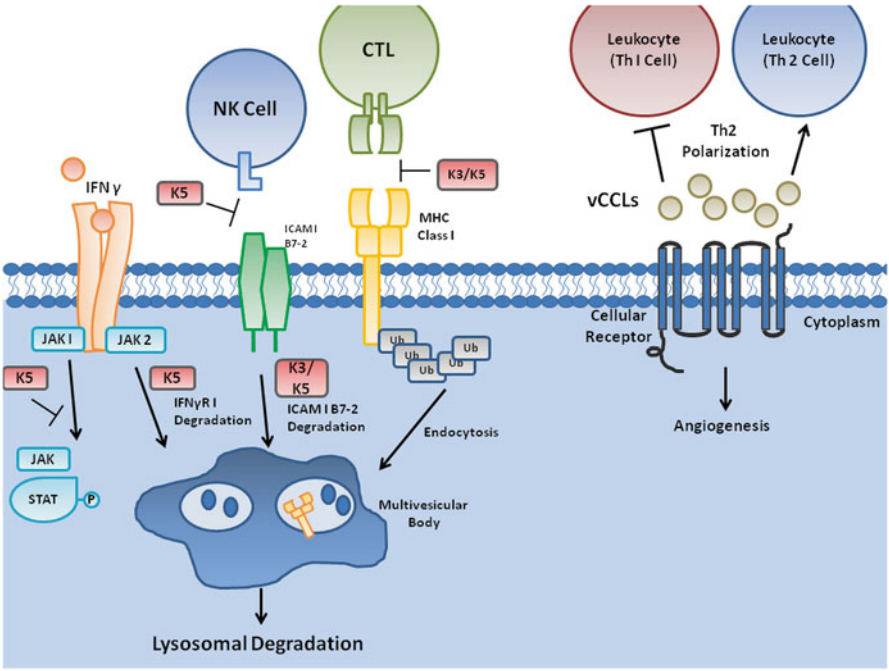

Fig. 12.5 The KSHV MIRs and vCCLs. K3 and K5 encode the KSHV MIRs, which can ubiquitinate and induce the degradation of a number of immune receptors including MHC class I, ICAM-1, B7-2, and IFN**γ**R1. The KSHV-encoded viral chemokines (vCCLs) block Th1 responses and augment Th2 responses

lysosomal destruction [234]. The MIRs also downregulate CD1d, an MHC-related protein that presents lipids and glycolipids to classical T and nonclassical NK T cells [235]. Additionally, K5/MIR2 (but not K3) can downregulate ICAM-1 and the costimulatory molecule B7-2 (CD86) [236, 237], which are proteins that exist on antigen-presenting cells and function in activating CD4-positive T cells. K5-driven downregulation of these proteins prevents helper T cell costimulation [236] and inhibits Natural Killer (NK) cell cytotoxicity [237]. Furthermore, K3 and K5 downregulate the interferon gamma receptor 1 (IFN-gammaR1) [238] and K5 reduces surface expression of the NKG2D ligands MHC class I-related chain A (MICA) and MICB, as well as the NKp80 ligand activation-induced C-type lectin (AICL) [239] (Fig. 12.5).

KSHV also encodes multiple CC chemokines: vCCL1 (formerly known as v-MIP-I), vCCL-2 (vMIP-II), and vCCL-3 (v-MIP-III) [240]. KSHV vCCL-1 signals through CCR8, vCCL-2 signals through CCR8 and CCR3, and vCCL-3 signals through CCR4 [241–243]. These viral chemokines activate receptors that are mainly present on Th2 cells, leading to a Th2-polarized response (Fig. 12.5). Moreover, vCCL-2 can interact with other chemokine receptors including CCR1, CCR2, CCR5, CXCR1, CXCR2, and CXCR4; however, binding of vCCL-2 to these

receptors inhibits, rather than activates, signal transduction in the presence of each receptor's chemokine ligands [241–243]. KS lesions comprise more Th2 T cells (CCR3+) than Th1 T cells (CCR5+) which aligns with these observations [244]. As well as binding T cell receptors, binding of vCCL-2 to CX3CR1 and CCR5 on NK cells inhibits binding to natural ligands resulting in reduced NK cell migration [245]. The viral chemokines can also induce angiogenic responses and activate vascular endothelial growth factor (VEGF) [246, 247].

Another viral protein that inhibits the inflammatory response is KSHV ORF63. This protein shows some homology to the nucleotide binding and oligomerization, leucine-rich repeat (NLR) family of proteins [248]. Activation of the NLR-dependent inflammasome complex results in the autocatalytic processing of procaspase-1 to caspase-1. Activated caspase-1 subsequently cleaves the precursors of the proinflammatory cytokines pro-IL-1β and pro-IL-18 into their biologically active forms: IL-1β and IL-18, respectively [249]. ORF63 binds NLRP1, and prevents its association with procaspase-1, thereby inhibiting the processing of procaspase-1 and subsequent processing of pro-IL-1β and pro-IL18 [248].

KSHV K14 encodes a glycoprotein of the immunoglobulin superfamily that shows homology to cellular CD200 (also known as OX2). Cellular CD200 is a negative regulator of inflammation [250]. One report demonstrated proinflammatory signaling by K14 [251], but other studies found that K14/vOX2 represses induction of myeloid activation by suppressing TNF-α production by activated macrophages, decreasing MCP-1 and IL8 production, and blocking the secretion of histamine from activated basophils [252, 253]. In human primary monocyte-derived macrophages, K14 expression decreases cytokine production and phagocytic activity only in the context of IFN-γ activation [254]. Expression of K14 in antigen presenting cells (APC) leads to the suppression of antigen-specific T-cell responses. These T cells make less IFN-γ and express less CD107a, a component of cytotoxic granules and an indication of cytotoxic killing after exposure to K14-expressing APC [255].

Viral Genes Involved in Cell Survival and Transformation

In addition to the genes and miRNAs described above in the section on viral latency, some other viral proteins that play roles in cell survival, signaling, and proliferation are described below and depicted in Fig. 12.6.

K1

K1 is a type I transmembrane protein located at the left end of the KSHV genome. K1 is found in the ER and on the cell membrane. Its amino terminus is glycosylated and the C-terminal cytoplasmic tail contains an immunoreceptor tyrosine-based

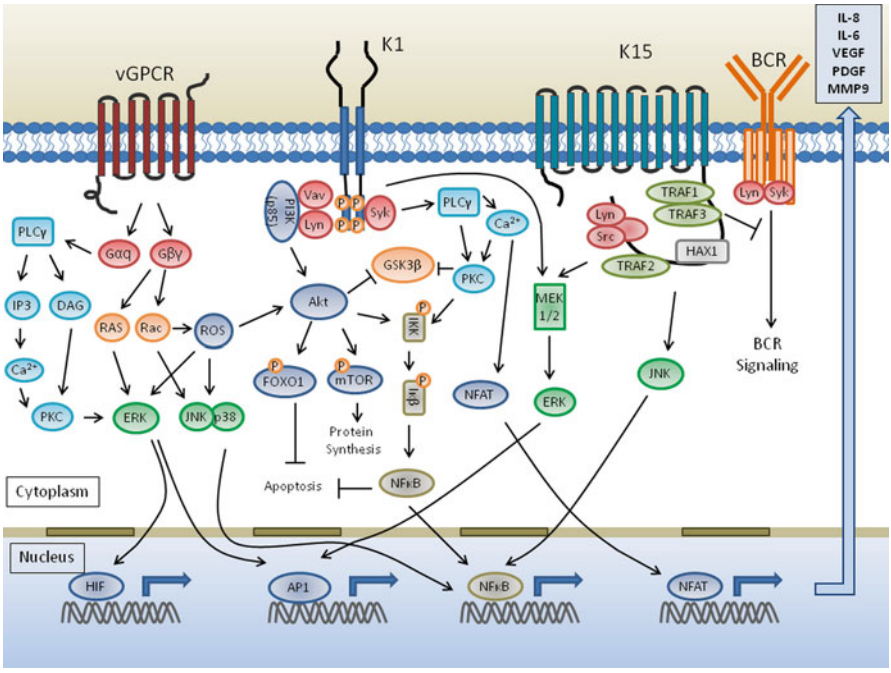

Fig. 12.6 The KSHV K1, K15, and vGPCR transmembrane proteins. Multiple cellular signal transduction pathways are activated by the expression of the viral proteins K1, K15, and vGPCR. These signaling pathways include MAPK, NF**κ**B, PI3K/Akt/mTOR, and PLC**γ**, and their activation leads to increased production of growth factors and cytokines, cell proliferation, and cell survival

activation motif (ITAM) [256] that when phosphorylated can activate downstream signaling events including PLCγ activation and calcium release [256, 257]. K1 is constitutively active and its aggregation leads to ITAM phosphorylation, Syk kinase recruitment, and increased NFATc and AP-1 activity. Moreover, the phosphorylated K1 tail can interact with Syk, PI3-kinase, lyn, RAS-GAP, PLC-γ 2, vav, and cbl [257–259]. PI3K activation results in the phosphorylation and activation of Akt kinase [259], the cell survival kinase involved in activation of pro-apoptotic factors, e.g., FOXO, Bad. K1-expressing cells are more resistant to apoptosis induced by Fas ligand or the expression of FOXO proteins [259]. K1 interacts with endoplasmic reticulum-associated Hsp40 (Erdj3/DnaJB11) and heat shock protein 90-beta (Hsp90beta), and these interactions are important for K1's effect on cell survival [260]. In B cells, K1 prevents surface transport of the B cell receptor (BCR) [261]. K1 has been shown to transform rodent fibroblasts [262] and K1 transgenic animals display lymphomas and sarcomas [263] and activated Lyn kinase [264]. K1 upregulates the secretion of angiogenic factors such as VEGF and matrix metalloproteinase-9 [265] in epithelial and endothelial cells. In addition to B cells, K1 can activate

the PI3K/Akt/mTOR pathway in endothelial cells, which results in immortalization of primary human umbilical vein endothelial cells (HUVEC) in culture [266]. Thus, K1 contributes to angiogenesis and cell survival.

vGPCR

KSHV encodes a viral G protein-coupled receptor (vGPCR) that is a member of the seven transmembrane G protein-coupled chemokine receptor family [267]. vGPCR displays constitutive signaling activity, although its activity can be augmented by chemokines such as GRO-α and inhibited by chemokines like CXCL10/IP10 [268, 269]. vGPCR signaling activates the PI3K/Akt/mTOR, NFκB, and MAPK pathways [270–277]. vGPCR augments angiogenesis and cell proliferation and vGPCR expression transforms cells [278–280]. vGPCR transgenic mice develop focal angioproliferative lesions similar to KS [281–283]. vGPCR is thought to aid transformation through a paracrine mechanism [284]. vGPCR activates IKKε leading to phosphorylation of NFκB. Nude mice injected with vGPCR-expressing cells deficient in IKKε fail to develop tumors suggesting that IKKε is essential for vGPCR-induced tumorigenesis [285]. vGPCR also activates expression of many cellular genes including Rac1 [286] and VEGF [271, 279].

K15

K15 lies at the right end of the viral genome and encodes another transmembrane signaling protein. K15 was initially named latency-associated membrane protein (LAMP) [287] and while it is thought to be expressed at low levels during latency [288], it is highly upregulated during the lytic cycle. K15 mRNAs are generated from alternatively spliced transcripts that include 8 or fewer exons resulting in four different isoforms [287, 289]. All spliced isoforms encode the carboxy-terminal cytoplasmic tail and are connected to a varying number of transmembrane domains. The full-length K15 protein contains 8 exons and 12 transmembrane domains. K15 localizes to the cell membrane and is often present in lipid rafts [290]. The K15 cytoplasmic region contains signaling motifs that, when phosphorylated, inhibit BCR signal transduction [289]. A TRAF-binding site in the cytoplasmic tail allows K15 to interact with TRAFs 1, 2, and 3 to constitutively activate NFκB and MAPK signaling pathways [287, 290]. K15 also contributes to angiogenesis. KSHV-infected endothelial cells induce the formation of angiogenic tubes upon reactivation; whereas, cells infected with K15-deficient KSHV fail to form tubes. K15 recruits PLCγ leading to the activation of calcineurin/NFAT-1 and increased expression of RCAN1, a gene involved in angiogenesis [291]. Finally, K15 can activate the expression of cytokines and chemokines including IL-8, IL-6, CXCL3, CCL20, CCL2, IL-1 α/β, and Cox-2 [292] (Fig. 12.6).

vIL-6

vIL-6 is a viral homolog of human IL-6 (hIL-6). It is different from hIL-6 since it does not need to bind to the gp80 subunit of the IL-6 receptor complex to initiate gp130 signal transduction [293–296]. vIL-6 contributes to pathogenesis by influencing multiple pathways and cellular proteins involved in proliferation, apoptosis, and angiogenesis. vIL-6 shares the anti-apoptotic functions of hIL-6 on B cells, and can prevent apoptosis in response to pro-apoptotic stimuli [297–299]. Depletion of vIL-6 in PEL cells inhibits cell growth [300]. vIL-6 can localize to the endoplasmic reticulum (ER) where it is thought to signal in an "intracrine" fashion. The interaction of vIL-6 and gp130 in the ER is important for maintaining PEL cell growth and viability via the activation of ERK 1 and 2 and STAT 1 and 3. vIL-6 also enhances the expression of DNA methyltransferase 1 (DNMT1) that induces irregular DNA methylation. Treating cells with a DNMT inhibitor results in reduced cell proliferation and migration [300–304]. vIL-6 can increase angiogenesis by upregulating VEGF [246, 305, 306]. Furthermore, vIL-6 expression induces angiopoietin 2, a proangiogenic and lymphangiogenic factor [307]. vIL6-expressing cells induce large tumors in mice and vIL6-transgenic mice develop MCD-like disease [308].

Conclusions

KSHV is an oncogenic herpesvirus associated with three different human malignancies. KSHV encodes an arsenal of viral proteins that help the virus evade the host immune response and stay hidden inside infected cells for the lifetime of the host. KSHV also encodes many viral proteins that can modulate cellular signaling pathways to facilitate angiogenesis, cell proliferation, and survival. By manipulating these cellular signaling pathways, KSHV creates an environment that is beneficial for the survival of the virus, which may inadvertently lead to transformation of the cell.

Acknowledgments We thank the Damania lab members for helpful discussions. B.D. is supported by NIH grants CA096500, 019014, AI107810, AI109965, DE018281, and DE023946. B.D. is a Leukemia & Lymphoma Society Scholar and a Burroughs Wellcome Fund Investigator in Infectious Disease. Due to space constraints, we apologize for not referencing many other publications in this chapter.

References

1. Chang Y, Cesarman E, Pessin MS, Lee F, Culpepper J, Knowles DM, et al. Identification of herpesvirus-like DNA sequences in AIDS-associated Kaposi's sarcoma. Science. 1994;266(5192):1865–9.
2. Cesarman E, Chang Y, Moore PS, Said JW, Knowles DM. Kaposi's sarcoma-associated herpesvirus-like DNA sequences in AIDS-related body-cavity-based lymphomas. N Engl J Med. 1995;332(18):1186–91.

3. Soulier J, Grollet L, Oksenhendler E, Cacoub P, Cazals-Hatem D, Babinet P, et al. Kaposi's sarcoma-associated herpesvirus-like DNA sequences in multicentric Castleman's disease. Blood. 1995;86(4):1276–80.
4. Uldrick TS, Wang V, O'Mahony D, Aleman K, Wyvill KM, Marshall V, et al. An interleukin-6-related systemic inflammatory syndrome in patients co-infected with Kaposi sarcoma-associated herpesvirus and HIV but without Multicentric Castleman disease. Clin Infect Dis. 2010;51(3):350–8. Epub 2010/06/30.
5. Polizzotto MN, Uldrick TS, Hu D, Yarchoan R. Clinical manifestations of Kaposi sarcoma herpesvirus lytic activation: multicentric Castleman disease (KSHV-MCD) and the KSHV inflammatory cytokine syndrome. Front Microbiol. 2012;3:73. Epub 2012/03/10.
6. Ensoli B, Sgadari C, Barillari G, Sirianni MC, Sturzl M, Monini P. Biology of Kaposi's sarcoma. Eur J Cancer. 2001;37(10):1251–69.
7. Wang HW, Trotter MW, Lagos D, Bourboulia D, Henderson S, Makinen T, et al. Kaposi sarcoma herpesvirus-induced cellular reprogramming contributes to the lymphatic endothelial gene expression in Kaposi sarcoma. Nat Genet. 2004;36(7):687–93.
8. Hong YK, Foreman K, Shin JW, Hirakawa S, Curry CL, Sage DR, et al. Lymphatic reprogramming of blood vascular endothelium by Kaposi sarcoma-associated herpesvirus. Nat Genet. 2004;36(7):683–5.
9. Carroll PA, Brazeau E, Lagunoff M. Kaposi's sarcoma-associated herpesvirus infection of blood endothelial cells induces lymphatic differentiation. Virology. 2004;328(1):7–18.
10. Hansen A, Henderson S, Lagos D, Nikitenko L, Coulter E, Roberts S, et al. KSHV-encoded miRNAs target MAF to induce endothelial cell reprogramming. Genes Dev. 2010;24(2): 195–205.
11. Kaposi M. Idiopathisches multiples Pigmentsarkom der Haut. Arch Dermatol Syph. 1872;4:265–73.
12. Antman K, Chang Y. Kaposi's sarcoma. N Engl J Med. 2000;342(14):1027–38.
13. Herndier B, Ganem D. The biology of Kaposi's sarcoma. Cancer Treat Res. 2001;104: 89–126.
14. Green I, Espiritu E, Ladanyi M, Chaponda R, Wieczorek R, Gallo L, et al. Primary lymphomatous effusions in AIDS: a morphological, immunophenotypic, and molecular study. Mod Pathol. 1995;8(1):39–45.
15. Knowles DM, Inghirami G, Ubriaco A, Dalla-Favera R. Molecular genetic analysis of three AIDS-associated neoplasms of uncertain lineage demonstrates their B-cell derivation and the possible pathogenetic role of the Epstein-Barr virus. Blood. 1989;73(3):792–9.
16. Du MQ, Liu H, Diss TC, Ye H, Hamoudi RA, Dupin N, et al. Kaposi sarcoma-associated herpesvirus infects monotypic (IgM lambda) but polyclonal naive B cells in Castleman disease and associated lymphoproliferative disorders. Blood. 2001;97(7):2130–6.
17. Zhu FX, Chong JM, Wu L, Yuan Y. Virion proteins of Kaposi's sarcoma-associated herpesvirus. J Virol. 2005;79(2):800–11.
18. Bechtel JT, Winant RC, Ganem D. Host and viral proteins in the virion of Kaposi's sarcoma-associated herpesvirus. J Virol. 2005;79(8):4952–64.
19. Bechtel J, Grundhoff A, Ganem D. RNAs in the virion of Kaposi's sarcoma-associated herpesvirus. J Virol. 2005;79(16):10138–46.
20. Trus BL, Heymann JB, Nealon K, Cheng N, Newcomb WW, Brown JC, et al. Capsid structure of Kaposi's sarcoma-associated herpesvirus, a gammaherpesvirus, compared to those of an alphaherpesvirus, herpes simplex virus type 1, and a betaherpesvirus, cytomegalovirus. J Virol. 2001;75(6):2879–90.
21. Nealon K, Newcomb WW, Pray TR, Craik CS, Brown JC, Kedes DH. Lytic replication of Kaposi's sarcoma-associated herpesvirus results in the formation of multiple capsid species: isolation and molecular characterization of A, B, and C capsids from a gammaherpesvirus. J Virol. 2001;75(6):2866–78.
22. Wu L, Lo P, Yu X, Stoops JK, Forghani B, Zhou ZH. Three-dimensional structure of the human herpesvirus 8 capsid. J Virol. 2000;74(20):9646–54.

23. Deng B, O'Connor CM, Kedes DH, Zhou ZH. Cryo-electron tomography of Kaposi's sarcoma-associated herpesvirus capsids reveals dynamic scaffolding structures essential to capsid assembly and maturation. J Struct Biol. 2008;161(3):419–27.
24. Deng B, O'Connor CM, Kedes DH, Zhou ZH. Direct visualization of the putative portal in the Kaposi's sarcoma-associated herpesvirus capsid by cryoelectron tomography. J Virol. 2007;81(7):3640–4.
25. Perkins EM, Anacker D, Davis A, Sankar V, Ambinder RF, Desai P. Small capsid protein pORF65 is essential for assembly of Kaposi's sarcoma-associated herpesvirus capsids. J Virol. 2008;82(14):7201–11. Epub 2008/05/09.
26. Renne R, Lagunoff M, Zhong W, Ganem D. The size and conformation of Kaposi's sarcoma-associated herpesvirus (human herpesvirus 8) DNA in infected cells and virions. J Virol. 1996;70(11):8151–4.
27. Neipel F, Albrecht JC, Fleckenstein B. Human herpesvirus 8–the first human Rhadinovirus. J Natl Cancer Inst Monogr. 1998;23:73–7.
28. Russo JJ, Bohenzky RA, Chien MC, Chen J, Yan M, Maddalena D, et al. Nucleotide sequence of the Kaposi sarcoma-associated herpesvirus (HHV8). Proc Natl Acad Sci U S A. 1996;93(25):14862–7.
29. Neipel F, Albrecht JC, Fleckenstein B. Cell-homologous genes in the Kaposi's sarcoma-associated rhadinovirus human herpesvirus 8: determinants of its pathogenicity? J Virol. 1997;71(6):4187–92.
30. Pfeffer S, Sewer A, Lagos-Quintana M, Sheridan R, Sander C, Grasser FA, et al. Identification of microRNAs of the herpesvirus family. Nat Methods. 2005;2(4):269–76.
31. Samols MA, Hu J, Skalsky RL, Renne R. Cloning and identification of a microRNA cluster within the latency-associated region of Kaposi's sarcoma-associated herpesvirus. J Virol. 2005;79(14):9301–5.
32. Cai X, Lu S, Zhang Z, Gonzalez CM, Damania B, Cullen BR. Kaposi's sarcoma-associated herpesvirus expresses an array of viral microRNAs in latently infected cells. Proc Natl Acad Sci U S A. 2005;102(15):5570–5.
33. Conrad NK, Steitz JA. A Kaposi's sarcoma virus RNA element that increases the nuclear abundance of intronless transcripts. EMBO J. 2005;24(10):1831–41.
34. Sun R, Lin SF, Gradoville L, Miller G. Polyadenylylated nuclear RNA encoded by Kaposi sarcoma-associated herpesvirus. Proc Natl Acad Sci U S A. 1996;93(21):11883–8.
35. Zhong W, Wang H, Herndier B, Ganem D. Restricted expression of Kaposi sarcoma-associated herpesvirus (human herpesvirus 8) genes in Kaposi sarcoma. Proc Natl Acad Sci U S A. 1996;93(13):6641–6.
36. Zhong W, Ganem D. Characterization of ribonucleoprotein complexes containing an abundant polyadenylated nuclear RNA encoded by Kaposi's sarcoma-associated herpesvirus (human herpesvirus 8). J Virol. 1997;71(2):1207–12.
37. Pertel PE. Human herpesvirus 8 glycoprotein B (gB), gH, and gL can mediate cell fusion. J Virol. 2002;76(9):4390–400.
38. Akula SM, Wang FZ, Vieira J, Chandran B. Human herpesvirus 8 interaction with target cells involves heparan sulfate. Virology. 2001;282(2):245–55.
39. Wang FZ, Akula SM, Sharma-Walia N, Zeng L, Chandran B. Human herpesvirus 8 envelope glycoprotein B mediates cell adhesion via its RGD sequence. J Virol. 2003;77(5):3131–47.
40. Naranatt PP, Akula SM, Zien CA, Krishnan HH, Chandran B. Kaposi's sarcoma-associated herpesvirus induces the phosphatidylinositol 3-kinase-PKC-zeta-MEK-ERK signaling pathway in target cells early during infection: implications for infectivity. J Virol. 2003;77(2):1524–39.
41. Hahn A, Birkmann A, Wies E, Dorer D, Mahr K, Sturzl M, et al. Kaposi's sarcoma-associated herpesvirus gH/gL: glycoprotein export and interaction with cellular receptors. J Virol. 2009;83(1):396–407.
42. Birkmann A, Mahr K, Ensser A, Yaguboglu S, Titgemeyer F, Fleckenstein B, et al. Cell surface heparan sulfate is a receptor for human herpesvirus 8 and interacts with envelope glycoprotein K8.1. J Virol. 2001;75(23):11583–93.

43. Akula SM, Pramod NP, Wang FZ, Chandran B. Integrin alpha3beta1 (CD 49c/29) is a cellular receptor for Kaposi's sarcoma-associated herpesvirus (KSHV/HHV-8) entry into the target cells. Cell. 2002;108(3):407–19.
44. Garrigues HJ, Rubinchikova YE, Dipersio CM, Rose TM. Integrin alphaVbeta3 Binds to the RGD motif of glycoprotein B of Kaposi's sarcoma-associated herpesvirus and functions as an RGD-dependent entry receptor. J Virol. 2008;82(3):1570–80.
45. Rappocciolo G, Hensler HR, Jais M, Reinhart TA, Pegu A, Jenkins FJ, et al. Human herpesvirus 8 infects and replicates in primary cultures of activated B lymphocytes through DC-SIGN. J Virol. 2008;82(10):4793–806.
46. Rappocciolo G, Jenkins FJ, Hensler HR, Piazza P, Jais M, Borowski L, et al. DC-SIGN is a receptor for human herpesvirus 8 on dendritic cells and macrophages. J Immunol. 2006;176(3):1741–9.
47. Kaleeba JA, Berger EA. Kaposi's sarcoma-associated herpesvirus fusion-entry receptor: cystine transporter xCT. Science. 2006;311(5769):1921–4.
48. Hahn AS, Kaufmann JK, Wies E, Naschberger E, Panteleev-Ivlev J, Schmidt K, et al. The ephrin receptor tyrosine kinase A2 is a cellular receptor for Kaposi's sarcoma-associated herpesvirus. Nat Med. 2012;18(6):961–6. Epub 2012/05/29.
49. Chakraborty S, Veettil MV, Bottero V, Chandran B. Kaposi's sarcoma-associated herpesvirus interacts with EphrinA2 receptor to amplify signaling essential for productive infection. Proc Natl Acad Sci U S A. 2012;109(19):E1163–72. Epub 2012/04/18.
50. Akula SM, Naranatt PP, Walia NS, Wang FZ, Fegley B, Chandran B. Kaposi's sarcoma-associated herpesvirus (human herpesvirus 8) infection of human fibroblast cells occurs through endocytosis. J Virol. 2003;77(14):7978–90.
51. Chandran B. Early events in Kaposi's sarcoma-associated herpesvirus infection of target cells. J Virol. 2010;84(5):2188–99.
52. Raghu H, Sharma-Walia N, Veettil MV, Sadagopan S, Chandran B. Kaposi's sarcoma-associated herpesvirus utilizes an actin polymerization-dependent macropinocytic pathway to enter human dermal microvascular endothelial and human umbilical vein endothelial cells. J Virol. 2009;83(10):4895–911.
53. Valiya Veettil M, Sadagopan S, Kerur N, Chakraborty S, Chandran B. Interaction of c-Cbl with myosin IIA regulates Bleb associated macropinocytosis of Kaposi's sarcoma-associated herpesvirus. PLoS Pathog. 2010;6(12):e1001238.
54. Krishnan HH, Sharma-Walia N, Streblow DN, Naranatt PP, Chandran B. Focal adhesion kinase is critical for entry of Kaposi's sarcoma-associated herpesvirus into target cells. J Virol. 2006;80(3):1167–80.
55. Raghu H, Sharma-Walia N, Veettil MV, Sadagopan S, Caballero A, Sivakumar R, et al. Lipid rafts of primary endothelial cells are essential for Kaposi's sarcoma-associated herpesvirus/human herpesvirus 8-induced phosphatidylinositol 3-kinase and RhoA-GTPases critical for microtubule dynamics and nuclear delivery of viral DNA but dispensable for binding and entry. J Virol. 2007;81(15):7941–59.
56. Pan H, Xie J, Ye F, Gao SJ. Modulation of Kaposi's sarcoma-associated herpesvirus infection and replication by MEK/ERK, JNK, and p38 multiple mitogen-activated protein kinase pathways during primary infection. J Virol. 2006;80(11):5371–82.
57. Naranatt PP, Krishnan HH, Smith MS, Chandran B. Kaposi's sarcoma-associated herpesvirus modulates microtubule dynamics via RhoA-GTP-diaphanous 2 signaling and utilizes the dynein motors to deliver its DNA to the nucleus. J Virol. 2005;79(2):1191–206.
58. Sharma-Walia N, Krishnan HH, Naranatt PP, Zeng L, Smith MS, Chandran B. ERK1/2 and MEK1/2 induced by Kaposi's sarcoma-associated herpesvirus (human herpesvirus 8) early during infection of target cells are essential for expression of viral genes and for establishment of infection. J Virol. 2005;79(16):10308–29.
59. Sharma-Walia N, Naranatt PP, Krishnan HH, Zeng L, Chandran B. Kaposi's sarcoma-associated herpesvirus/human herpesvirus 8 envelope glycoprotein gB induces the integrin-dependent focal adhesion kinase-Src-phosphatidylinositol 3-kinase-rho GTPase signal pathways and cytoskeletal rearrangements. J Virol. 2004;78(8):4207–23.

60. Sadagopan S, Sharma-Walia N, Veettil MV, Raghu H, Sivakumar R, Bottero V, et al. Kaposi's sarcoma-associated herpesvirus induces sustained NF-kappaB activation during de novo infection of primary human dermal microvascular endothelial cells that is essential for viral gene expression. J Virol. 2007;81(8):3949–68.
61. Veettil MV, Sharma-Walia N, Sadagopan S, Raghu H, Sivakumar R, Naranatt PP, et al. RhoA-GTPase facilitates entry of Kaposi's sarcoma-associated herpesvirus into adherent target cells in a Src-dependent manner. J Virol. 2006;80(23):11432–46.
62. Xie J, Pan H, Yoo S, Gao SJ. Kaposi's sarcoma-associated herpesvirus induction of AP-1 and interleukin 6 during primary infection mediated by multiple mitogen-activated protein kinase pathways. J Virol. 2005;79(24):15027–37.
63. Yoo SM, Zhou FC, Ye FC, Pan HY, Gao SJ. Early and sustained expression of latent and host modulating genes in coordinated transcriptional program of KSHV productive primary infection of human primary endothelial cells. Virology. 2005;343(1):47–64.
64. Naranatt PP, Krishnan HH, Svojanovsky SR, Bloomer C, Mathur S, Chandran B. Host gene induction and transcriptional reprogramming in Kaposi's sarcoma-associated herpesvirus (KSHV/HHV-8)-infected endothelial, fibroblast, and B cells: insights into modulation events early during infection. Cancer Res. 2004;64(1):72–84.
65. West JA, Gregory SM, Sivaraman V, Su L, Damania B. Activation of plasmacytoid dendritic cells by Kaposi's sarcoma-associated herpesvirus. J Virol. 2011;85(2):895–904.
66. Greene W, Gao SJ. Actin dynamics regulate multiple endosomal steps during Kaposi's sarcoma-associated herpesvirus entry and trafficking in endothelial cells. PLoS Pathog. 2009;5(7):e1000512.
67. Inoue N, Winter J, Lal RB, Offermann MK, Koyano S. Characterization of entry mechanisms of human herpesvirus 8 by using an Rta-dependent reporter cell line. J Virol. 2003;77(14): 8147–52.
68. Jarousse N, Chandran B, Coscoy L. Lack of heparan sulfate expression in B-cell lines: implications for Kaposi's sarcoma-associated herpesvirus and murine gammaherpesvirus 68 infections. J Virol. 2008;82(24):12591–7.
69. Kaleeba JA, Berger EA. Broad target cell selectivity of Kaposi's sarcoma-associated herpesvirus glycoprotein-mediated cell fusion and virion entry. Virology. 2006;354(1):7–14.
70. Kliche S, Kremmer E, Hammerschmidt W, Koszinowski U, Haas J. Persistent infection of Epstein-Barr virus-positive B lymphocytes by human herpesvirus 8. J Virol. 1998;72(10): 8143–9.
71. Krishnan HH, Naranatt PP, Smith MS, Zeng L, Bloomer C, Chandran B. Concurrent expression of latent and a limited number of lytic genes with immune modulation and antiapoptotic function by Kaposi's sarcoma-associated herpesvirus early during infection of primary endothelial and fibroblast cells and subsequent decline of lytic gene expression. J Virol. 2004;78(7):3601–20.
72. Lagunoff M, Bechtel J, Venetsanakos E, Roy AM, Abbey N, Herndier B, et al. De novo infection and serial transmission of Kaposi's sarcoma-associated herpesvirus in cultured endothelial cells. J Virol. 2002;76(5):2440–8.
73. Renne R, Blackbourn D, Whitby D, Levy J, Ganem D. Limited transmission of Kaposi's sarcoma-associated herpesvirus in cultured cells. J Virol. 1998;72(6):5182–8.
74. Hassman LM, Ellison TJ, Kedes DH. KSHV infects a subset of human tonsillar B cells, driving proliferation and plasmablast differentiation. J Clin Invest. 2011;121(2):752–68.
75. West J, Damania B. Upregulation of the TLR3 pathway by Kaposi's sarcoma-associated herpesvirus during primary infection. J Virol. 2008;82(11):5440–9.
76. Ambroziak JA, Blackbourn DJ, Herndier BG, Glogau RG, Gullett JH, McDonald AR, et al. Herpes-like sequences in HIV-infected and uninfected Kaposi's sarcoma patients. Science. 1995;268(5210):582–3.
77. Dupin N, Fisher C, Kellam P, Ariad S, Tulliez M, Franck N, et al. Distribution of human herpesvirus-8 latently infected cells in Kaposi's sarcoma, multicentric Castleman's disease, and primary effusion lymphoma. Proc Natl Acad Sci U S A. 1999;96(8):4546–51.

78. Parravicini C, Chandran B, Corbellino M, Berti E, Paulli M, Moore PS, et al. Differential viral protein expression in Kaposi's sarcoma-associated herpesvirus-infected diseases: Kaposi's sarcoma, primary effusion lymphoma, and multicentric Castleman's disease. Am J Pathol. 2000;156(3):743–9.
79. Foreman KE, Bacon PE, Hsi ED, Nickoloff BJ. In situ polymerase chain reaction-based localization studies support role of human herpesvirus-8 as the cause of two AIDS-related neoplasms: Kaposi's sarcoma and body cavity lymphoma. J Clin Invest. 1997;99(12): 2971–8. Epub 1997/06/15.
80. Reed JA, Nador RG, Spaulding D, Tani Y, Cesarman E, Knowles DM. Demonstration of Kaposi's sarcoma-associated herpes virus cyclin D homolog in cutaneous Kaposi's sarcoma by colorimetric in situ hybridization using a catalyzed signal amplification system. Blood. 1998;91(10):3825–32. Epub 1998/06/20.
81. Staskus KA, Zhong W, Gebhard K, Herndier B, Wang H, Renne R, et al. Kaposi's sarcoma-associated herpesvirus gene expression in endothelial (spindle) tumor cells. J Virol. 1997;71(1):715–9. Epub 1997/01/01.
82. Blasig C, Zietz C, Haar B, Neipel F, Esser S, Brockmeyer NH, et al. Monocytes in Kaposi's sarcoma lesions are productively infected by human herpesvirus 8. J Virol. 1997;71(10): 7963–8.
83. Sun R, Lin SF, Gradoville L, Yuan Y, Zhu F, Miller G. A viral gene that activates lytic cycle expression of Kaposi's sarcoma-associated herpesvirus. Proc Natl Acad Sci U S A. 1998;95(18):10866–71.
84. Lukac DM, Kirshner JR, Ganem D. Transcriptional activation by the product of open reading frame 50 of Kaposi's sarcoma-associated herpesvirus is required for lytic viral reactivation in B cells. J Virol. 1999;73(11):9348–61.
85. Yu Y, Black JB, Goldsmith CS, Browning PJ, Bhalla K, Offermann MK. Induction of human herpesvirus-8 DNA replication and transcription by butyrate and TPA in BCBL-1 cells. J Gen Virol. 1999;80(Pt 1):83–90.
86. Mercader M, Taddeo B, Panella JR, Chandran B, Nickoloff BJ, Foreman KE. Induction of HHV-8 lytic cycle replication by inflammatory cytokines produced by HIV-1-infected T cells. Am J Pathol. 2000;156(6):1961–71.
87. Chang J, Renne R, Dittmer D, Ganem D. Inflammatory cytokines and the reactivation of Kaposi's sarcoma-associated herpesvirus lytic replication. Virology. 2000;266(1):17–25.
88. Wilson SJ, Tsao EH, Webb BL, Ye H, Dalton-Griffin L, Tsantoulas C, et al. X box binding protein XBP-1s transactivates the Kaposi's sarcoma-associated herpesvirus (KSHV) ORF50 promoter, linking plasma cell differentiation to KSHV reactivation from latency. J Virol. 2007;81(24):13578–86.
89. Yu F, Feng J, Harada JN, Chanda SK, Kenney SC, Sun R. B cell terminal differentiation factor XBP-1 induces reactivation of Kaposi's sarcoma-associated herpesvirus. FEBS Lett. 2007;581(18):3485–8.
90. Gregory SM, West JA, Dillon PJ, Hilscher C, Dittmer DP, Damania B. Toll-like receptor signaling controls reactivation of KSHV from latency. Proc Natl Acad Sci U S A. 2009;106(28):11725–30.
91. Dillon PJ, Gregory SM, Tamburro K, Sanders MK, Johnson GL, Raab-Traub N, et al. Tousled-like kinases modulate reactivation of gammaherpesviruses from latency. Cell Host Microbe. 2013;13(2):204–14. Epub 2013/02/19.
92. Chen HS, Wikramasinghe P, Showe L, Lieberman PM. Cohesins repress Kaposi's sarcoma-associated herpesvirus immediate early gene transcription during latency. J Virol. 2012;86(17):9454–64. Epub 2012/06/29.
93. Vieira J, Huang ML, Koelle DM, Corey L. Transmissible Kaposi's sarcoma-associated herpesvirus (human herpesvirus 8) in saliva of men with a history of Kaposi's sarcoma. J Virol. 1997;71(9):7083–7.
94. Pauk J, Huang ML, Brodie SJ, Wald A, Koelle DM, Schacker T, et al. Mucosal shedding of human herpesvirus 8 in men. N Engl J Med. 2000;343(19):1369–77.

95. Casper C, Redman M, Huang ML, Pauk J, Lampinen TM, Hawes SE, et al. HIV infection and human herpesvirus-8 oral shedding among men who have sex with men. J Acquir Immune Defic Syndr. 2004;35(3):233–8.
96. Duus KM, Lentchitsky V, Wagenaar T, Grose C, Webster-Cyriaque J. Wild-type Kaposi's sarcoma-associated herpesvirus isolated from the oropharynx of immune-competent individuals has tropism for cultured oral epithelial cells. J Virol. 2004;78(8):4074–84.
97. Casper C, Krantz E, Selke S, Kuntz SR, Wang J, Huang ML, et al. Frequent and asymptomatic oropharyngeal shedding of human herpesvirus 8 among immunocompetent men. J Infect Dis. 2007;195(1):30–6. Epub 2006/12/08.
98. Dittmer D, Lagunoff M, Renne R, Staskus K, Haase A, Ganem D. A cluster of latently expressed genes in Kaposi's sarcoma-associated herpesvirus. J Virol. 1998;72(10):8309–15.
99. Sarid R, Flore O, Bohenzky RA, Chang Y, Moore PS. Transcription mapping of the Kaposi's sarcoma-associated herpesvirus (human herpesvirus 8) genome in a body cavity-based lymphoma cell line (BC-1). J Virol. 1998;72(2):1005–12.
100. Talbot SJ, Weiss RA, Kellam P, Boshoff C. Transcriptional analysis of human herpesvirus-8 open reading frames 71, 72, 73, K14, and 74 in a primary effusion lymphoma cell line. Virology. 1999;257(1):84–94.
101. Pearce M, Matsumura S, Wilson AC. Transcripts encoding K12, v-FLIP, v-cyclin, and the microRNA cluster of Kaposi's sarcoma-associated herpesvirus originate from a common promoter. J Virol. 2005;79(22):14457–64.
102. Cai X, Cullen BR. Transcriptional origin of Kaposi's sarcoma-associated herpesvirus microRNAs. J Virol. 2006;80(5):2234–42.
103. Grundhoff A, Sullivan CS, Ganem D. A combined computational and microarray-based approach identifies novel microRNAs encoded by human gamma-herpesviruses. RNA. 2006;12(5):733–50.
104. Fakhari FD, Dittmer DP. Charting latency transcripts in Kaposi's sarcoma-associated herpesvirus by whole-genome real-time quantitative PCR. J Virol. 2002;76(12):6213–23.
105. Dittmer DP. Transcription profile of Kaposi's sarcoma-associated herpesvirus in primary Kaposi's sarcoma lesions as determined by real-time PCR arrays. Cancer Res. 2003;63(9): 2010–5.
106. Rivas C, Thlick AE, Parravicini C, Moore PS, Chang Y. Kaposi's sarcoma-associated herpesvirus LANA2 is a B-cell-specific latent viral protein that inhibits p53. J Virol. 2001;75(1): 429–38.
107. Ballestas ME, Chatis PA, Kaye KM. Efficient persistence of extrachromosomal KSHV DNA mediated by latency-associated nuclear antigen. Science. 1999;284(5414):641–4.
108. Ballestas ME, Kaye KM. Kaposi's sarcoma-associated herpesvirus latency-associated nuclear antigen 1 mediates episome persistence through cis-acting terminal repeat (TR) sequence and specifically binds TR DNA. J Virol. 2001;75(7):3250–8.
109. Cotter 2nd MA, Robertson ES. The latency-associated nuclear antigen tethers the Kaposi's sarcoma-associated herpesvirus genome to host chromosomes in body cavity-based lymphoma cells. Virology. 1999;264(2):254–64.
110. Cotter 2nd MA, Subramanian C, Robertson ES. The Kaposi's sarcoma-associated herpesvirus latency-associated nuclear antigen binds to specific sequences at the left end of the viral genome through its carboxy-terminus. Virology. 2001;291(2):241–59.
111. Garber AC, Hu J, Renne R. Latency-associated nuclear antigen (LANA) cooperatively binds to two sites within the terminal repeat, and both sites contribute to the ability of LANA to suppress transcription and to facilitate DNA replication. J Biol Chem. 2002;277(30): 27401–11.
112. Garber AC, Shu MA, Hu J, Renne R. DNA binding and modulation of gene expression by the latency-associated nuclear antigen of Kaposi's sarcoma-associated herpesvirus. J Virol. 2001;75(17):7882–92.
113. Barbera AJ, Ballestas ME, Kaye KM. The Kaposi's sarcoma-associated herpesvirus latency-associated nuclear antigen 1N terminus is essential for chromosome association, DNA replication, and episome persistence. J Virol. 2004;78(1):294–301.

114. Piolot T, Tramier M, Coppey M, Nicolas JC, Marechal V. Close but distinct regions of human herpesvirus 8 latency-associated nuclear antigen 1 are responsible for nuclear targeting and binding to human mitotic chromosomes. J Virol. 2001;75(8):3948–59.
115. Barbera AJ, Chodaparambil JV, Kelley-Clarke B, Joukov V, Walter JC, Luger K, et al. The nucleosomal surface as a docking station for Kaposi's sarcoma herpesvirus LANA. Science. 2006;311(5762):856–61.
116. Watanabe T, Sugaya M, Atkins AM, Aquilino EA, Yang A, Borris DL, et al. Kaposi's sarcoma-associated herpesvirus latency-associated nuclear antigen prolongs the life span of primary human umbilical vein endothelial cells. J Virol. 2003;77(11):6188–96.
117. Fakhari FD, Jeong JH, Kanan Y, Dittmer DP. The latency-associated nuclear antigen of Kaposi sarcoma-associated herpesvirus induces B cell hyperplasia and lymphoma. J Clin Invest. 2006;116(3):735–42.
118. Sin SH, Fakhari FD, Dittmer DP. The viral latency-associated nuclear antigen augments the B-cell response to antigen in vivo. J Virol. 2010;84(20):10653–60.
119. Friborg Jr J, Kong W, Hottiger MO, Nabel GJ. p53 inhibition by the LANA protein of KSHV protects against cell death. Nature. 1999;402(6764):889–94.
120. Petre CE, Sin SH, Dittmer DP. Functional p53 signaling in Kaposi's sarcoma-associated herpesvirus lymphomas: implications for therapy. J Virol. 2007;81(4):1912–22.
121. Radkov SA, Kellam P, Boshoff C. The latent nuclear antigen of Kaposi sarcoma-associated herpesvirus targets the retinoblastoma-E2F pathway and with the oncogene Hras transforms primary rat cells. Nat Med. 2000;6(10):1121–7.
122. Fujimuro M, Wu FY, ApRhys C, Kajumbula H, Young DB, Hayward GS, et al. A novel viral mechanism for dysregulation of beta-catenin in Kaposi's sarcoma-associated herpesvirus latency. Nat Med. 2003;9(3):300–6.
123. Bubman D, Guasparri I, Cesarman E. Deregulation of c-Myc in primary effusion lymphoma by Kaposi's sarcoma herpesvirus latency-associated nuclear antigen. Oncogene. 2007;26(34): 4979–86.
124. Liu J, Martin HJ, Liao G, Hayward SD. The Kaposi's sarcoma-associated herpesvirus LANA protein stabilizes and activates c-Myc. J Virol. 2007;81(19):10451–9.
125. Sun Z, Xiao B, Jha HC, Lu J, Banerjee S, Robertson ES. KSHV encoded LANA can induce chromosomal instability through targeted degradation of the mitotic checkpoint kinase Bub1. J Virol. 2014. Epub 2014/04/18.
126. Renne R, Barry C, Dittmer D, Compitello N, Brown PO, Ganem D. Modulation of cellular and viral gene expression by the latency-associated nuclear antigen of Kaposi's sarcoma-associated herpesvirus. J Virol. 2001;75(1):458–68.
127. An FQ, Compitello N, Horwitz E, Sramkoski M, Knudsen ES, Renne R. The latency-associated nuclear antigen of Kaposi's sarcoma-associated herpesvirus modulates cellular gene expression and protects lymphoid cells from p16 INK4A-induced cell cycle arrest. J Biol Chem. 2005;280(5):3862–74.
128. Wong LY, Matchett GA, Wilson AC. Transcriptional activation by the Kaposi's sarcoma-associated herpesvirus latency-associated nuclear antigen is facilitated by an N-terminal chromatin-binding motif. J Virol. 2004;78(18):10074–85.
129. Krithivas A, Young DB, Liao G, Greene D, Hayward SD. Human herpesvirus 8 LANA interacts with proteins of the mSin3 corepressor complex and negatively regulates Epstein-Barr virus gene expression in dually infected PEL cells. J Virol. 2000;74(20):9637–45.
130. Schwam DR, Luciano RL, Mahajan SS, Wong L, Wilson AC. Carboxy terminus of human herpesvirus 8 latency-associated nuclear antigen mediates dimerization, transcriptional repression, and targeting to nuclear bodies. J Virol. 2000;74(18):8532–40.
131. Lan K, Kuppers DA, Robertson ES. Kaposi's sarcoma-associated herpesvirus reactivation is regulated by interaction of latency-associated nuclear antigen with recombination signal sequence-binding protein Jkappa, the major downstream effector of the Notch signaling pathway. J Virol. 2005;79(6):3468–78.
132. Cai Q, Cai S, Zhu C, Verma SC, Choi JY, Robertson ES. A unique SUMO-2-interacting motif within LANA is essential for KSHV latency. PLoS Pathog. 2013;9(11):e1003750. Epub 2013/11/28.

133. Sun R, Liang D, Gao Y, Lan K. Kaposi's sarcoma-associated herpesvirus-encoded LANA interacts with host KAP1 to facilitate establishment of viral latency. J Virol. 2014. Epub 2014/04/18.
134. Chang Y, Moore PS, Talbot SJ, Boshoff CH, Zarkowska T, Godden K, et al. Cyclin encoded by KS herpesvirus. Nature. 1996;382(6590):410.
135. Godden-Kent D, Talbot SJ, Boshoff C, Chang Y, Moore P, Weiss RA, et al. The cyclin encoded by Kaposi's sarcoma-associated herpesvirus stimulates cdk6 to phosphorylate the retinoblastoma protein and histone H1. J Virol. 1997;71(6):4193–8.
136. Li M, Lee H, Yoon DW, Albrecht JC, Fleckenstein B, Neipel F, et al. Kaposi's sarcoma-associated herpesvirus encodes a functional cyclin. J Virol. 1997;71(3):1984–91.
137. Cuomo ME, Knebel A, Morrice N, Paterson H, Cohen P, Mittnacht S. p53-Driven apoptosis limits centrosome amplification and genomic instability downstream of NPM1 phosphorylation. Nat Cell Biol. 2008;10(6):723–30.
138. Swanton C, Mann DJ, Fleckenstein B, Neipel F, Peters G, Jones N. Herpes viral cyclin/Cdk6 complexes evade inhibition by CDK inhibitor proteins. Nature. 1997;390(6656):184–7.
139. Mann DJ, Child ES, Swanton C, Laman H, Jones N. Modulation of p27(Kip1) levels by the cyclin encoded by Kaposi's sarcoma-associated herpesvirus. EMBO J. 1999;18(3):654–63.
140. Ellis M, Chew YP, Fallis L, Freddersdorf S, Boshoff C, Weiss RA, et al. Degradation of p27(Kip) cdk inhibitor triggered by Kaposi's sarcoma virus cyclin-cdk6 complex. EMBO J. 1999;18(3):644–53.
141. Zhi H, Zahoor MA, Shudofsky AM, Giam CZ. KSHV vCyclin counters the senescence/G1 arrest response triggered by NF-kappaB hyperactivation. Oncogene. 2014. Epub 2014/01/29.
142. Chang PC, Li M. Kaposi's sarcoma-associated herpesvirus K-cyclin interacts with Cdk9 and stimulates Cdk9-mediated phosphorylation of p53 tumor suppressor. J Virol. 2008;82(1): 278–90.
143. Verschuren EW, Hodgson JG, Gray JW, Kogan S, Jones N, Evan GI. The role of p53 in suppression of KSHV cyclin-induced lymphomagenesis. Cancer Res. 2004;64(2):581–9.
144. Verschuren EW, Klefstrom J, Evan GI, Jones N. The oncogenic potential of Kaposi's sarcoma-associated herpesvirus cyclin is exposed by p53 loss in vitro and in vivo. Cancer Cell. 2002;2(3):229–41.
145. Sugaya M, Watanabe T, Yang A, Starost MF, Kobayashi H, Atkins AM, et al. Lymphatic dysfunction in transgenic mice expressing KSHV k-cyclin under the control of the VEGFR-3 promoter. Blood. 2005;105(6):2356–63.
146. Jones T, Ramos da Silva S, Bedolla R, Ye F, Zhou F, Gao SJ. Viral cyclin promotes KSHV-induced cellular transformation and tumorigenesis by overriding contact inhibition. Cell Cycle. 2014;13(5):845–58. Epub 2014/01/15.
147. Belanger C, Gravel A, Tomoiu A, Janelle ME, Gosselin J, Tremblay MJ, et al. Human herpesvirus 8 viral FLICE-inhibitory protein inhibits Fas-mediated apoptosis through binding and prevention of procaspase-8 maturation. J Hum Virol. 2001;4(2):62–73.
148. Djerbi M, Screpanti V, Catrina AI, Bogen B, Biberfeld P, Grandien A. The inhibitor of death receptor signaling, FLICE-inhibitory protein defines a new class of tumor progression factors. J Exp Med. 1999;190(7):1025–32.
149. Ballon G, Chen K, Perez R, Tam W, Cesarman E. Kaposi sarcoma herpesvirus (KSHV) vFLIP oncoprotein induces B cell transdifferentiation and tumorigenesis in mice. J Clin Invest. 2011;121(3):1141–53.
150. Chugh P, Matta H, Schamus S, Zachariah S, Kumar A, Richardson JA, et al. Constitutive NF-kappaB activation, normal Fas-induced apoptosis, and increased incidence of lymphoma in human herpes virus 8K13 transgenic mice. Proc Natl Acad Sci U S A. 2005;102(36): 12885–90.
151. Sun Q, Zachariah S, Chaudhary PM. The human herpes virus 8-encoded viral FLICE-inhibitory protein induces cellular transformation via NF-kappaB activation. J Biol Chem. 2003;278(52):52437–45.

152. Matta H, Sun Q, Moses G, Chaudhary PM. Molecular genetic analysis of human herpes virus 8-encoded viral FLICE inhibitory protein-induced NF-kappaB activation. J Biol Chem. 2003;278(52):52406–11.
153. Sun Q, Matta H, Chaudhary PM. The human herpes virus 8-encoded viral FLICE inhibitory protein protects against growth factor withdrawal-induced apoptosis via NF-kappa B activation. Blood. 2003;101(5):1956–61.
154. Chaudhary PM, Jasmin A, Eby MT, Hood L. Modulation of the NF-kappa B pathway by virally encoded death effector domains-containing proteins. Oncogene. 1999;18(42):5738–46.
155. Guasparri I, Keller SA, Cesarman E. KSHV vFLIP is essential for the survival of infected lymphoma cells. J Exp Med. 2004;199(7):993–1003.
156. Field N, Low W, Daniels M, Howell S, Daviet L, Boshoff C, et al. KSHV vFLIP binds to IKK-gamma to activate IKK. J Cell Sci. 2003;116(Pt 18):3721–8.
157. Liu L, Eby MT, Rathore N, Sinha SK, Kumar A, Chaudhary PM. The human herpes virus 8-encoded viral FLICE inhibitory protein physically associates with and persistently activates the Ikappa B kinase complex. J Biol Chem. 2002;277(16):13745–51.
158. Guasparri I, Wu H, Cesarman E. The KSHV oncoprotein vFLIP contains a TRAF-interacting motif and requires TRAF2 and TRAF3 for signalling. EMBO Rep. 2006;7(1):114–9.
159. Matta H, Chaudhary PM. Activation of alternative NF-kappa B pathway by human herpes virus 8-encoded Fas-associated death domain-like IL-1 beta-converting enzyme inhibitory protein (vFLIP). Proc Natl Acad Sci U S A. 2004;101(25):9399–404.
160. Tolani B, Matta H, Gopalakrishnan R, Punj V, Chaudhary PM. NEMO is essential for KSHV-encoded vFLIP K13-induced gene expression and protection against death receptor-induced cell death and its N-terminal 251 residues are sufficient for this process. J Virol. 2014. Epub 2014/03/29.
161. Forero A, Moore PS, Sarkar SN. Role of IRF4 in IFN-stimulated gene induction and maintenance of Kaposi sarcoma-associated herpesvirus latency in primary effusion lymphoma cells. J Immunol. 2013;191(3):1476–85. Epub 2013/06/28.
162. Singh VV, Kerur N, Bottero V, Dutta S, Chakraborty S, Ansari MA, et al. Kaposi's sarcoma-associated herpesvirus latency in endothelial and B cells activates gamma interferon-inducible protein 16-mediated inflammasomes. J Virol. 2013;87(8):4417–31. Epub 2013/02/08.
163. Graham C, Matta H, Yang Y, Yi H, Suo Y, Tolani B, et al. Kaposi's sarcoma-associated herpesvirus oncoprotein K13 protects against B cell receptor-induced growth arrest and apoptosis through NF-kappaB activation. J Virol. 2013;87(4):2242–52. Epub 2012/12/14.
164. Ahmad A, Groshong JS, Matta H, Schamus S, Punj V, Robinson LJ, et al. Kaposi sarcoma-associated herpesvirus-encoded viral FLICE inhibitory protein (vFLIP) K13 cooperates with Myc to promote lymphoma in mice. Cancer Biol Ther. 2010;10(10):1033–40.
165. Sadler R, Wu L, Forghani B, Renne R, Zhong W, Herndier B, et al. A complex translational program generates multiple novel proteins from the latently expressed kaposin (K12) locus of Kaposi's sarcoma-associated herpesvirus. J Virol. 1999;73(7):5722–30.
166. Muralidhar S, Pumfery AM, Hassani M, Sadaie MR, Kishishita M, Brady JN, et al. Identification of kaposin (open reading frame K12) as a human herpesvirus 8 (Kaposi's sarcoma-associated herpesvirus) transforming gene. J Virol. 1998;72(6):4980–8.
167. Kliche S, Nagel W, Kremmer E, Atzler C, Ege A, Knorr T, et al. Signaling by human herpesvirus 8 kaposin A through direct membrane recruitment of cytohesin-1. Mol Cell. 2001;7(4):833–43.
168. McCormick C, Ganem D. The kaposin B protein of KSHV activates the p38/MK2 pathway and stabilizes cytokine mRNAs. Science. 2005;307(5710):739–41.
169. King CA. Kaposi's sarcoma-associated herpesvirus kaposin B induces unique monophosphorylation of STAT3 at serine 727 and MK2-mediated inactivation of the STAT3 transcriptional repressor TRIM28. J Virol. 2013;87(15):8779–91. Epub 2013/06/07.
170. Umbach JL, Cullen BR. In-depth analysis of Kaposi's sarcoma-associated herpesvirus microRNA expression provides insights into the mammalian microRNA-processing machinery. J Virol. 2010;84(2):695–703. Epub 2009/11/06.

171. Bellare P, Ganem D. Regulation of KSHV lytic switch protein expression by a virus-encoded microRNA: an evolutionary adaptation that fine-tunes lytic reactivation. Cell Host Microbe. 2009;6(6):570–5.
172. Samols MA, Skalsky RL, Maldonado AM, Riva A, Lopez MC, Baker HV, et al. Identification of cellular genes targeted by KSHV-encoded microRNAs. PLoS Pathog. 2007;3(5):e65.
173. Skalsky RL, Samols MA, Plaisance KB, Boss IW, Riva A, Lopez MC, et al. Kaposi's sarcoma-associated herpesvirus encodes an ortholog of miR-155. J Virol. 2007;81(23): 12836–45.
174. Gottwein E, Cullen BR. A human herpesvirus microRNA inhibits p21 expression and attenuates p21-mediated cell cycle arrest. J Virol. 2010;84(10):5229–37.
175. Sin SH, Kim YB, Dittmer DP. Latency locus complements MicroRNA 155 deficiency in vivo. J Virol. 2013;87(21):11908–11. doi:10.1128/JVI.01620-13. Epub 2013 Aug 21.
176. Lei X, Bai Z, Ye F, Xie J, Kim CG, Huang Y, et al. Regulation of NF-kappaB inhibitor IkappaBalpha and viral replication by a KSHV microRNA. Nat Cell Biol. 2010;12(2): 193–9.
177. Moody R, Zhu Y, Huang Y, Cui X, Jones T, Bedolla R, et al. KSHV microRNAs mediate cellular transformation and tumorigenesis by redundantly targeting cell growth and survival pathways. PLoS Pathog. 2013;9(12):e1003857. Epub 2014/01/05.
178. Abend JR, Ramalingam D, Kieffer-Kwon P, Uldrick TS, Yarchoan R, Ziegelbauer JM. Kaposi's sarcoma-associated herpesvirus microRNAs target IRAK1 and MYD88, two components of the toll-like receptor/interleukin-1R signaling cascade, to reduce inflammatory-cytokine expression. J Virol. 2012;86(21):11663–74. Epub 2012/08/17.
179. Gallaher AM, Das S, Xiao Z, Andresson T, Kieffer-Kwon P, Happel C, et al. Proteomic screening of human targets of viral microRNAs reveals functions associated with immune evasion and angiogenesis. PLoS Pathog. 2013;9(9):e1003584. Epub 2013/09/17.
180. Gradoville L, Gerlach J, Grogan E, Shedd D, Nikiforow S, Metroka C, et al. Kaposi's sarcoma-associated herpesvirus open reading frame 50/Rta protein activates the entire viral lytic cycle in the HH-B2 primary effusion lymphoma cell line. J Virol. 2000;74(13): 6207–12.
181. Lukac DM, Renne R, Kirshner JR, Ganem D. Reactivation of Kaposi's sarcoma-associated herpesvirus infection from latency by expression of the ORF 50 transactivator, a homolog of the EBV R protein. Virology. 1998;252(2):304–12.
182. Xu Y, AuCoin DP, Huete AR, Cei SA, Hanson LJ, Pari GS. A Kaposi's sarcoma-associated herpesvirus/human herpesvirus 8 ORF50 deletion mutant is defective for reactivation of latent virus and DNA replication. J Virol. 2005;79(6):3479–87.
183. Seaman WT, Ye D, Wang RX, Hale EE, Weisse M, Quinlivan EB. Gene expression from the ORF50/K8 region of Kaposi's sarcoma-associated herpesvirus. Virology. 1999;263(2): 436–49.
184. Zhu FX, Cusano T, Yuan Y. Identification of the immediate-early transcripts of Kaposi's sarcoma-associated herpesvirus. J Virol. 1999;73(7):5556–67.
185. Sun R, Lin SF, Staskus K, Gradoville L, Grogan E, Haase A, et al. Kinetics of Kaposi's sarcoma-associated herpesvirus gene expression. J Virol. 1999;73(3):2232–42.
186. Lu F, Zhou J, Wiedmer A, Madden K, Yuan Y, Lieberman PM. Chromatin remodeling of the Kaposi's sarcoma-associated herpesvirus ORF50 promoter correlates with reactivation from latency. J Virol. 2003;77(21):11425–35.
187. Chen J, Ueda K, Sakakibara S, Okuno T, Parravicini C, Corbellino M, et al. Activation of latent Kaposi's sarcoma-associated herpesvirus by demethylation of the promoter of the lytic transactivator. Proc Natl Acad Sci U S A. 2001;98(7):4119–24.
188. Chen J, Ye F, Xie J, Kuhne K, Gao SJ. Genome-wide identification of binding sites for Kaposi's sarcoma-associated herpesvirus lytic switch protein, RTA. Virology. 2009;386(2): 290–302.
189. Liang Y, Ganem D. RBP-J (CSL) is essential for activation of the K14/vGPCR promoter of Kaposi's sarcoma-associated herpesvirus by the lytic switch protein RTA. J Virol. 2004;78(13):6818–26.

190. Wang SE, Wu FY, Fujimuro M, Zong J, Hayward SD, Hayward GS. Role of CCAAT/enhancer-binding protein alpha (C/EBPalpha) in activation of the Kaposi's sarcoma-associated herpesvirus (KSHV) lytic-cycle replication-associated protein (RAP) promoter in cooperation with the KSHV replication and transcription activator (RTA) and RAP. J Virol. 2003;77(1):600–23.
191. Deng H, Chu JT, Rettig MB, Martinez-Maza O, Sun R. Rta of the human herpesvirus 8/Kaposi sarcoma-associated herpesvirus up-regulates human interleukin-6 gene expression. Blood. 2002;100(5):1919–21.
192. Liang Y, Chang J, Lynch SJ, Lukac DM, Ganem D. The lytic switch protein of KSHV activates gene expression via functional interaction with RBP-Jkappa (CSL), the target of the Notch signaling pathway. Genes Dev. 2002;16(15):1977–89.
193. Deng H, Song MJ, Chu JT, Sun R. Transcriptional regulation of the interleukin-6 gene of human herpesvirus 8 (Kaposi's sarcoma-associated herpesvirus). J Virol. 2002;76(16):8252–64.
194. Lukac DM, Garibyan L, Kirshner JR, Palmeri D, Ganem D. DNA binding by Kaposi's sarcoma-associated herpesvirus lytic switch protein is necessary for transcriptional activation of two viral delayed early promoters. J Virol. 2001;75(15):6786–99.
195. Chen J, Ueda K, Sakakibara S, Okuno T, Yamanishi K. Transcriptional regulation of the Kaposi's sarcoma-associated herpesvirus viral interferon regulatory factor gene. J Virol. 2000;74(18):8623–34.
196. Wang Y, Yuan Y. Essential role of RBP-Jkappa in activation of the K8 delayed-early promoter of Kaposi's sarcoma-associated herpesvirus by ORF50/RTA. Virology. 2007;359(1):19–27.
197. Wen HJ, Minhas V, Wood C. Identification and characterization of a new Kaposi's sarcoma-associated herpesvirus replication and transcription activator (RTA)-responsive element involved in RTA-mediated transactivation. J Gen Virol. 2009;90(Pt 4):944–53.
198. Jeong J, Papin J, Dittmer D. Differential regulation of the overlapping Kaposi's sarcoma-associated herpesvirus vGCR (orf74) and LANA (orf73) promoters. J Virol. 2001;75(4):1798–807.
199. Ziegelbauer J, Grundhoff A, Ganem D. Exploring the DNA binding interactions of the Kaposi's sarcoma-associated herpesvirus lytic switch protein by selective amplification of bound sequences in vitro. J Virol. 2006;80(6):2958–67.
200. Matsumura S, Fujita Y, Gomez E, Tanese N, Wilson AC. Activation of the Kaposi's sarcoma-associated herpesvirus major latency locus by the lytic switch protein RTA (ORF50). J Virol. 2005;79(13):8493–505.
201. Wang Y, Chong OT, Yuan Y. Differential regulation of K8 gene expression in immediate-early and delayed-early stages of Kaposi's sarcoma-associated herpesvirus. Virology. 2004;325(1):149–63.
202. Wang SE, Wu FY, Yu Y, Hayward GS. CCAAT/enhancer-binding protein-alpha is induced during the early stages of Kaposi's sarcoma-associated herpesvirus (KSHV) lytic cycle reactivation and together with the KSHV replication and transcription activator (RTA) cooperatively stimulates the viral RTA, MTA, and PAN promoters. J Virol. 2003;77(17):9590–612.
203. Sakakibara S, Ueda K, Chen J, Okuno T, Yamanishi K. Octamer-binding sequence is a key element for the autoregulation of Kaposi's sarcoma-associated herpesvirus ORF50/Lyta gene expression. J Virol. 2001;75(15):6894–900.
204. Gwack Y, Hwang S, Lim C, Won YS, Lee CH, Choe J. Kaposi's Sarcoma-associated herpesvirus open reading frame 50 stimulates the transcriptional activity of STAT3. J Biol Chem. 2002;277(8):6438–42.
205. Gwack Y, Byun H, Hwang S, Lim C, Choe J. CREB-binding protein and histone deacetylase regulate the transcriptional activity of Kaposi's sarcoma-associated herpesvirus open reading frame 50. J Virol. 2001;75(4):1909–17.
206. Gwack Y, Baek HJ, Nakamura H, Lee SH, Meisterernst M, Roeder RG, et al. Principal role of TRAP/mediator and SWI/SNF complexes in Kaposi's sarcoma-associated herpesvirus RTA-mediated lytic reactivation. Mol Cell Biol. 2003;23(6):2055–67.

207. Dalton-Griffin L, Wilson SJ, Kellam P. X-box binding protein 1 contributes to induction of the Kaposi's sarcoma-associated herpesvirus lytic cycle under hypoxic conditions. J Virol. 2009;83(14):7202–9.
208. AuCoin DP, Colletti KS, Cei SA, Papouskova I, Tarrant M, Pari GS. Amplification of the Kaposi's sarcoma-associated herpesvirus/human herpesvirus 8 lytic origin of DNA replication is dependent upon a cis-acting AT-rich region and an ORF50 response element and the trans-acting factors ORF50 (K-Rta) and K8 (K-bZIP). Virology. 2004;318(2):542–55.
209. Lin CL, Li H, Wang Y, Zhu FX, Kudchodkar S, Yuan Y. Kaposi's sarcoma-associated herpesvirus lytic origin (ori-Lyt)-dependent DNA replication: identification of the ori-Lyt and association of K8 bZip protein with the origin. J Virol. 2003;77(10):5578–88.
210. Wu FY, Ahn JH, Alcendor DJ, Jang WJ, Xiao J, Hayward SD, et al. Origin-independent assembly of Kaposi's sarcoma-associated herpesvirus DNA replication compartments in transient cotransfection assays and association with the ORF-K8 protein and cellular PML. J Virol. 2001;75(3):1487–506.
211. Lu M, Suen J, Frias C, Pfeiffer R, Tsai MH, Chuang E, et al. Dissection of the Kaposi's sarcoma-associated herpesvirus gene expression program by using the viral DNA replication inhibitor cidofovir. J Virol. 2004;78(24):13637–52.
212. Jenner RG, Alba MM, Boshoff C, Kellam P. Kaposi's sarcoma-associated herpesvirus latent and lytic gene expression as revealed by DNA arrays. J Virol. 2001;75(2):891–902.
213. Akira S, Takeda K. Toll-like receptor signalling. Nat Rev Immunol. 2004;4(7):499–511.
214. Kerur N, Veettil MV, Sharma-Walia N, Bottero V, Sadagopan S, Otageri P, et al. IFI16 acts as a nuclear pathogen sensor to induce the inflammasome in response to Kaposi Sarcoma-associated herpesvirus infection. Cell Host Microbe. 2011;9(5):363–75. Epub 2011/05/18.
215. West J, Wicks M, Gregory SM, Chugh P, Jacobs SR, Zhang Z, Host KM, Dittmer DP, Damania B. An important role for mitochondrial antiviral signaling protein in the Kaposi's sarcoma-associated herpesvirus life cycle. J Virol. 2014;88(10):5778–87. Epub 2014 Mar 12.
216. Zimring JC, Goodbourn S, Offermann MK. Human herpesvirus 8 encodes an interferon regulatory factor (IRF) homolog that represses IRF-1-mediated transcription. J Virol. 1998; 72(1):701–7.
217. Burysek L, Yeow WS, Lubyova B, Kellum M, Schafer SL, Huang YQ, et al. Functional analysis of human herpesvirus 8-encoded viral interferon regulatory factor 1 and its association with cellular interferon regulatory factors and p300. J Virol. 1999;73(9):7334–42.
218. Gao SJ, Boshoff C, Jayachandra S, Weiss RA, Chang Y, Moore PS. KSHV ORF K9 (vIRF) is an oncogene which inhibits the interferon signaling pathway. Oncogene. 1997;15(16): 1979–85.
219. Lin R, Genin P, Mamane Y, Sgarbanti M, Battistini A, Harrington Jr WJ, et al. HHV-8 encoded vIRF-1 represses the interferon antiviral response by blocking IRF-3 recruitment of the CBP/p300 coactivators. Oncogene. 2001;20(7):800–11.
220. Li M, Damania B, Alvarez X, Ogryzko V, Ozato K, Jung JU. Inhibition of p300 histone acetyltransferase by viral interferon regulatory factor. Mol Cell Biol. 2000;20(21):8254–63.
221. Fuld S, Cunningham C, Klucher K, Davison AJ, Blackbourn DJ. Inhibition of interferon signaling by the Kaposi's sarcoma-associated herpesvirus full-length viral interferon regulatory factor 2 protein. J Virol. 2006;80(6):3092–7.
222. Areste C, Mutocheluh M, Blackbourn DJ. Identification of caspase-mediated decay of interferon regulatory factor-3, exploited by a Kaposi sarcoma-associated herpesvirus immunoregulatory protein. J Biol Chem. 2009;284(35):23272–85.
223. Lubyova B, Pitha PM. Characterization of a novel human herpesvirus 8-encoded protein, vIRF-3, that shows homology to viral and cellular interferon regulatory factors. J Virol. 2000;74(17):8194–201.
224. Joo CH, Shin YC, Gack M, Wu L, Levy D, Jung JU. Inhibition of interferon regulatory factor 7 (IRF7)-mediated interferon signal transduction by the Kaposi's sarcoma-associated herpesvirus viral IRF homolog vIRF3. J Virol. 2007;81(15):8282–92.

225. Lubyova B, Kellum MJ, Frisancho AJ, Pitha PM. Kaposi's sarcoma-associated herpesvirus-encoded vIRF-3 stimulates the transcriptional activity of cellular IRF-3 and IRF-7. J Biol Chem. 2004;279(9):7643–54.
226. Schmidt K, Wies E, Neipel F. Kaposi's sarcoma-associated herpesvirus viral interferon regulatory factor 3 inhibits gamma interferon and major histocompatibility complex class II expression. J Virol. 2011;85(9):4530–7. Epub 2011/02/25.
227. Zhu FX, King SM, Smith EJ, Levy DE, Yuan Y. A Kaposi's sarcoma-associated herpesviral protein inhibits virus-mediated induction of type I interferon by blocking IRF-7 phosphorylation and nuclear accumulation. Proc Natl Acad Sci U S A. 2002;99(8):5573–8.
228. Yu Y, Wang SE, Hayward GS. The KSHV immediate-early transcription factor RTA encodes ubiquitin E3 ligase activity that targets IRF7 for proteosome-mediated degradation. Immunity. 2005;22(1):59–70.
229. Zhu FX, Li X, Zhou F, Gao SJ, Yuan Y. Functional characterization of Kaposi's sarcoma-associated herpesvirus ORF45 by bacterial artificial chromosome-based mutagenesis. J Virol. 2006;80(24):12187–96.
230. Zhu FX, Sathish N, Yuan Y. Antagonism of host antiviral responses by Kaposi's sarcoma-associated herpesvirus tegument protein ORF45. PLoS One. 2010;5(5):e10573.
231. Coscoy L, Ganem D. Kaposi's sarcoma-associated herpesvirus encodes two proteins that block cell surface display of MHC class I chains by enhancing their endocytosis. Proc Natl Acad Sci U S A. 2000;97(14):8051–6.
232. Stevenson PG, Efstathiou S, Doherty PC, Lehner PJ. Inhibition of MHC class I-restricted antigen presentation by gamma 2-herpesviruses. Proc Natl Acad Sci U S A. 2000;97(15): 8455–60.
233. Ishido S, Wang C, Lee BS, Cohen GB, Jung JU. Downregulation of major histocompatibility complex class I molecules by Kaposi's sarcoma-associated herpesvirus K3 and K5 proteins. J Virol. 2000;74(11):5300–9.
234. Bartee E, Mansouri M, Hovey Nerenberg BT, Gouveia K, Fruh K. Downregulation of major histocompatibility complex class I by human ubiquitin ligases related to viral immune evasion proteins. J Virol. 2004;78(3):1109–20.
235. Sanchez DJ, Gumperz JE, Ganem D. Regulation of CD1d expression and function by a herpesvirus infection. J Clin Invest. 2005;115(5):1369–78. Epub 2005/05/03.
236. Coscoy L, Ganem D. A viral protein that selectively downregulates ICAM-1 and B7-2 and modulates T cell costimulation. J Clin Invest. 2001;107(12):1599–606.
237. Ishido S, Choi JK, Lee BS, Wang C, DeMaria M, Johnson RP, et al. Inhibition of natural killer cell-mediated cytotoxicity by Kaposi's sarcoma-associated herpesvirus K5 protein. Immunity. 2000;13(3):365–74.
238. Li Q, Means R, Lang S, Jung JU. Downregulation of gamma interferon receptor 1 by Kaposi's sarcoma-associated herpesvirus K3 and K5. J Virol. 2007;81(5):2117–27.
239. Thomas M, Boname JM, Field S, Nejentsev S, Salio M, Cerundolo V, et al. Down-regulation of NKG2D and NKp80 ligands by Kaposi's sarcoma-associated herpesvirus K5 protects against NK cell cytotoxicity. Proc Natl Acad Sci U S A. 2008;105(5):1656–61.
240. Nicholas J, Ruvolo VR, Burns WH, Sandford G, Wan X, Ciufo D, et al. Kaposi's sarcoma-associated human herpesvirus-8 encodes homologues of macrophage inflammatory protein-1 and interleukin-6. Nat Med. 1997;3(3):287–92.
241. Nicholas J. Human gammaherpesvirus cytokines and chemokine receptors. J Interferon Cytokine Res. 2005;25(7):373–83.
242. Stine JT, Wood C, Hill M, Epp A, Raport CJ, Schweickart VL, et al. KSHV-encoded CC chemokine vMIP-III is a CCR4 agonist, stimulates angiogenesis, and selectively chemoattracts TH2 cells. Blood. 2000;95(4):1151–7.
243. Endres MJ, Garlisi CG, Xiao H, Shan L, Hedrick JA. The Kaposi's sarcoma-related herpesvirus (KSHV)-encoded chemokine vMIP-I is a specific agonist for the CC chemokine receptor (CCR)8. J Exp Med. 1999;189(12):1993–8.

244. Weber KS, Grone HJ, Rocken M, Klier C, Gu S, Wank R, et al. Selective recruitment of Th2-type cells and evasion from a cytotoxic immune response mediated by viral macrophage inhibitory protein-II. Eur J Immunol. 2001;31(8):2458–66.
245. Yamin R, Kaynan NS, Glasner A, Vitenshtein A, Tsukerman P, Bauman Y, et al. The viral KSHV chemokine vMIP-II inhibits the migration of Naive and activated human NK cells by antagonizing two distinct chemokine receptors. PLoS Pathog. 2013;9(8):e1003568. Epub 2013/08/24.
246. Liu C, Okruzhnov Y, Li H, Nicholas J. Human herpesvirus 8 (HHV-8)-encoded cytokines induce expression of and autocrine signaling by vascular endothelial growth factor (VEGF) in HHV-8-infected primary-effusion lymphoma cell lines and mediate VEGF-independent antiapoptotic effects. J Virol. 2001;75(22):10933–40.
247. Boshoff C, Endo Y, Collins PD, Takeuchi Y, Reeves JD, Schweickart VL, et al. Angiogenic and HIV-inhibitory functions of KSHV-encoded chemokines. Science. 1997;278(5336): 290–4.
248. Gregory SM, Davis BK, West JA, Taxman DJ, Matsuzawa S, Reed JC, et al. Discovery of a viral NLR homolog that inhibits the inflammasome. Science. 2011;331(6015):330–4.
249. Kanneganti TD. Central roles of NLRs and inflammasomes in viral infection. Nat Rev Immunol. 2010;10(10):688–98.
250. Hoek RM, Ruuls SR, Murphy CA, Wright GJ, Goddard R, Zurawski SM, et al. Down-regulation of the macrophage lineage through interaction with OX2 (CD200). Science. 2000;290(5497):1768–71.
251. Chung YH, Means RE, Choi JK, Lee BS, Jung JU. Kaposi's sarcoma-associated herpesvirus OX2 glycoprotein activates myeloid-lineage cells to induce inflammatory cytokine production. J Virol. 2002;76(10):4688–98.
252. Foster-Cuevas M, Wright GJ, Puklavec MJ, Brown MH, Barclay AN. Human herpesvirus 8K14 protein mimics CD200 in down-regulating macrophage activation through CD200 receptor. J Virol. 2004;78(14):7667–76.
253. Rezaee SA, Gracie JA, McInnes IB, Blackbourn DJ. Inhibition of neutrophil function by the Kaposi's sarcoma-associated herpesvirus vOX2 protein. AIDS. 2005;19(16):1907–10.
254. Salata C, Curtarello M, Calistri A, Sartori E, Sette P, de Bernard M, et al. vOX2 glycoprotein of human herpesvirus 8 modulates human primary macrophages activity. J Cell Physiol. 2009;219(3):698–706.
255. Misstear K, Chanas SA, Rezaee SA, Colman R, Quinn LL, Long HM, et al. Suppression of antigen-specific T cell responses by the Kaposi's sarcoma-associated herpesvirus viral OX2 protein and its cellular orthologue, CD200. J Virol. 2012;86(11):6246–57. Epub 2012/04/12.
256. Lee H, Guo J, Li M, Choi JK, DeMaria M, Rosenzweig M, et al. Identification of an immunoreceptor tyrosine-based activation motif of K1 transforming protein of Kaposi's sarcoma-associated herpesvirus. Mol Cell Biol. 1998;18(9):5219–28.
257. Lagunoff M, Majeti R, Weiss A, Ganem D. Deregulated signal transduction by the K1 gene product of Kaposi's sarcoma-associated herpesvirus. Proc Natl Acad Sci U S A. 1999;96(10):5704–9.
258. Lee BS, Lee SH, Feng P, Chang H, Cho NH, Jung JU. Characterization of the Kaposi's sarcoma-associated herpesvirus K1 signalosome. J Virol. 2005;79(19):12173–84.
259. Tomlinson CC, Damania B. The K1 protein of Kaposi's sarcoma-associated herpesvirus activates the Akt signaling pathway. J Virol. 2004;78(4):1918–27.
260. Wen KW, Damania B. Hsp90 and Hsp40/Erdj3 are required for the expression and anti-apoptotic function of KSHV K1. Oncogene. 2010;29(24):3532–44.
261. Lee BS, Alvarez X, Ishido S, Lackner AA, Jung JU. Inhibition of intracellular transport of B cell antigen receptor complexes by Kaposi's sarcoma-associated herpesvirus K1. J Exp Med. 2000;192(1):11–21.
262. Lee H, Veazey R, Williams K, Li M, Guo J, Neipel F, et al. Deregulation of cell growth by the K1 gene of Kaposi's sarcoma-associated herpesvirus. Nat Med. 1998;4(4):435–40.

263. Prakash O, Tang ZY, Peng X, Coleman R, Gill J, Farr G, et al. Tumorigenesis and aberrant signaling in transgenic mice expressing the human herpesvirus-8K1 gene. J Natl Cancer Inst. 2002;94(12):926–35.
264. Prakash O, Swamy OR, Peng X, Tang ZY, Li L, Larson JE, et al. Activation of Src kinase Lyn by the Kaposi sarcoma-associated herpesvirus K1 protein: implications for lymphomagenesis. Blood. 2005;105(10):3987–94.
265. Wang L, Wakisaka N, Tomlinson CC, DeWire SM, Krall S, Pagano JS, et al. The Kaposi's sarcoma-associated herpesvirus (KSHV/HHV-8) K1 protein induces expression of angiogenic and invasion factors. Cancer Res. 2004;64(8):2774–81.
266. Wang L, Dittmer DP, Tomlinson CC, Fakhari FD, Damania B. Immortalization of primary endothelial cells by the K1 protein of Kaposi's sarcoma-associated herpesvirus. Cancer Res. 2006;66(7):3658–66.
267. Cesarman E, Nador RG, Bai F, Bohenzky RA, Russo JJ, Moore PS, et al. Kaposi's sarcoma-associated herpesvirus contains G protein-coupled receptor and cyclin D homologs which are expressed in Kaposi's sarcoma and malignant lymphoma. J Virol. 1996;70(11):8218–23.
268. Gershengorn MC, Geras-Raaka E, Varma A, Clark-Lewis I. Chemokines activate Kaposi's sarcoma-associated herpesvirus G protein-coupled receptor in mammalian cells in culture. J Clin Invest. 1998;102(8):1469–72.
269. Arvanitakis L, Geras-Raaka E, Varma A, Gershengorn MC, Cesarman E. Human herpesvirus KSHV encodes a constitutively active G-protein-coupled receptor linked to cell proliferation. Nature. 1997;385(6614):347–50.
270. Smit MJ, Verzijl D, Casarosa P, Navis M, Timmerman H, Leurs R. Kaposi's sarcoma-associated herpesvirus-encoded G protein-coupled receptor ORF74 constitutively activates p44/p42 MAPK and Akt via G(i) and phospholipase C-dependent signaling pathways. J Virol. 2002;76(4):1744–52.
271. Sodhi A, Montaner S, Patel V, Zohar M, Bais C, Mesri EA, et al. The Kaposi's sarcoma-associated herpes virus G protein-coupled receptor up-regulates vascular endothelial growth factor expression and secretion through mitogen-activated protein kinase and p38 pathways acting on hypoxia-inducible factor 1alpha. Cancer Res. 2000;60(17):4873–80.
272. Sodhi A, Chaisuparat R, Hu J, Ramsdell AK, Manning BD, Sausville EA, et al. The TSC2/mTOR pathway drives endothelial cell transformation induced by the Kaposi's sarcoma-associated herpesvirus G protein-coupled receptor. Cancer Cell. 2006;10(2):133–43.
273. Sodhi A, Montaner S, Patel V, Gomez-Roman JJ, Li Y, Sausville EA, et al. Akt plays a central role in sarcomagenesis induced by Kaposi's sarcoma herpesvirus-encoded G protein-coupled receptor. Proc Natl Acad Sci U S A. 2004;101(14):4821–6.
274. Montaner S, Sodhi A, Pece S, Mesri EA, Gutkind JS. The Kaposi's sarcoma-associated herpesvirus G protein-coupled receptor promotes endothelial cell survival through the activation of Akt/protein kinase B. Cancer Res. 2001;61(6):2641–8.
275. Cannon M, Philpott NJ, Cesarman E. The Kaposi's sarcoma-associated herpesvirus G protein-coupled receptor has broad signaling effects in primary effusion lymphoma cells. J Virol. 2003;77(1):57–67.
276. Schwarz M, Murphy PM. Kaposi's sarcoma-associated herpesvirus G protein-coupled receptor constitutively activates NF-kappa B and induces proinflammatory cytokine and chemokine production via a C-terminal signaling determinant. J Immunol. 2001;167(1):505–13.
277. Martin D, Galisteo R, Ji Y, Montaner S, Gutkind JS. An NF-kappaB gene expression signature contributes to Kaposi's sarcoma virus vGPCR-induced direct and paracrine neoplasia. Oncogene. 2008;27(13):1844–52.
278. Hanson J. Standardization of proximal femur BMD measurements. International Committee for Standards in Bone Measurement. Osteoporos Int. 1997;7(5):500–1.
279. Bais C, Van Geelen A, Eroles P, Mutlu A, Chiozzini C, Dias S, et al. Kaposi's sarcoma associated herpesvirus G protein-coupled receptor immortalizes human endothelial cells by activation of the VEGF receptor-2/KDR. Cancer Cell. 2003;3(2):131–43.

280. Bais C, Santomasso B, Coso O, Arvanitakis L, Raaka EG, Gutkind JS, et al. G-protein-coupled receptor of Kaposi's sarcoma-associated herpesvirus is a viral oncogene and angiogenesis activator. Nature. 1998;391(6662):86–9.
281. Guo HG, Sadowska M, Reid W, Tschachler E, Hayward G, Reitz M. Kaposi's sarcoma-like tumors in a human herpesvirus 8 ORF74 transgenic mouse. J Virol. 2003;77(4):2631–9.
282. Montaner S, Sodhi A, Molinolo A, Bugge TH, Sawai ET, He Y, et al. Endothelial infection with KSHV genes in vivo reveals that vGPCR initiates Kaposi's sarcomagenesis and can promote the tumorigenic potential of viral latent genes. Cancer Cell. 2003;3(1):23–36.
283. Yang TY, Chen SC, Leach MW, Manfra D, Homey B, Wiekowski M, et al. Transgenic expression of the chemokine receptor encoded by human herpesvirus 8 induces an angioproliferative disease resembling Kaposi's sarcoma. J Exp Med. 2000;191(3):445–54.
284. Cesarman E, Mesri EA, Gershengorn MC. Viral G protein-coupled receptor and Kaposi's sarcoma: a model of paracrine neoplasia? J Exp Med. 2000;191(3):417–22.
285. Wang Y, Lu X, Zhu L, Shen Y, Chengedza S, Feng H, et al. IKK epsilon kinase is crucial for viral G protein-coupled receptor tumorigenesis. Proc Natl Acad Sci U S A. 2013; 110(27):11139–44. Epub 2013/06/19.
286. Montaner S, Sodhi A, Servitja JM, Ramsdell AK, Barac A, Sawai ET, et al. The small GTPase Rac1 links the Kaposi sarcoma-associated herpesvirus vGPCR to cytokine secretion and paracrine neoplasia. Blood. 2004;104(9):2903–11.
287. Glenn M, Rainbow L, Aurade F, Davison A, Schulz TF. Identification of a spliced gene from Kaposi's sarcoma-associated herpesvirus encoding a protein with similarities to latent membrane proteins 1 and 2A of Epstein-Barr virus. J Virol. 1999;73(8):6953–63.
288. Sharp TV, Wang HW, Koumi A, Hollyman D, Endo Y, Ye H, et al. K15 protein of Kaposi's sarcoma-associated herpesvirus is latently expressed and binds to HAX-1, a protein with antiapoptotic function. J Virol. 2002;76(2):802–16.
289. Choi JK, Lee BS, Shim SN, Li M, Jung JU. Identification of the novel K15 gene at the rightmost end of the Kaposi's sarcoma-associated herpesvirus genome. J Virol. 2000;74(1): 436–46.
290. Brinkmann MM, Glenn M, Rainbow L, Kieser A, Henke-Gendo C, Schulz TF. Activation of mitogen-activated protein kinase and NF-kappaB pathways by a Kaposi's sarcoma-associated herpesvirus K15 membrane protein. J Virol. 2003;77(17):9346–58.
291. Bala K, Bosco R, Gramolelli S, Haas DA, Kati S, Pietrek M, et al. Kaposi's sarcoma herpesvirus K15 protein contributes to virus-induced angiogenesis by recruiting PLCgamma1 and activating NFAT1-dependent RCAN1 expression. PLoS Pathog. 2012;8(9):e1002927. Epub 2012/10/03.
292. Brinkmann MM, Pietrek M, Dittrich-Breiholz O, Kracht M, Schulz TF. Modulation of host gene expression by the K15 protein of Kaposi's sarcoma-associated herpesvirus. J Virol. 2007;81(1):42–58.
293. Breen EC, Gage JR, Guo B, Magpantay L, Narazaki M, Kishimoto T, et al. Viral interleukin 6 stimulates human peripheral blood B cells that are unresponsive to human interleukin 6. Cell Immunol. 2001;212(2):118–25.
294. Li H, Wang H, Nicholas J. Detection of direct binding of human herpesvirus 8-encoded interleukin-6 (vIL-6) to both gp130 and IL-6 receptor (IL-6R) and identification of amino acid residues of vIL-6 important for IL-6R-dependent and -independent signaling. J Virol. 2001;75(7):3325–34.
295. Li H, Nicholas J. Identification of amino acid residues of gp130 signal transducer and gp80 alpha receptor subunit that are involved in ligand binding and signaling by human herpesvirus 8-encoded interleukin-6. J Virol. 2002;76(11):5627–36.
296. Hu F, Nicholas J. Signal transduction by human herpesvirus 8 viral interleukin-6 (vIL-6) is modulated by the nonsignaling gp80 subunit of the IL-6 receptor complex and is distinct from signaling induced by human IL-6. J Virol. 2006;80(21):10874–8.
297. Jones KD, Aoki Y, Chang Y, Moore PS, Yarchoan R, Tosato G. Involvement of interleukin-10 (IL-10) and viral IL-6 in the spontaneous growth of Kaposi's sarcoma herpesvirus-associated infected primary effusion lymphoma cells. Blood. 1999;94(8):2871–9.

298. Oksenhendler E, Boulanger E, Galicier L, Du MQ, Dupin N, Diss TC, et al. High incidence of Kaposi sarcoma-associated herpesvirus-related non-Hodgkin lymphoma in patients with HIV infection and multicentric Castleman disease. Blood. 2002;99(7):2331–6.
299. Parravicini C, Corbellino M, Paulli M, Magrini U, Lazzarino M, Moore PS, et al. Expression of a virus-derived cytokine, KSHV vIL-6, in HIV-seronegative Castleman's disease. Am J Pathol. 1997;151(6):1517–22.
300. Chen D, Sandford G, Nicholas J. Intracellular signaling mechanisms and activities of human herpesvirus 8 interleukin-6. J Virol. 2009;83(2):722–33. Epub 2008/11/07.
301. Meads MB, Medveczky PG. Kaposi's sarcoma-associated herpesvirus-encoded viral interleukin-6 is secreted and modified differently than human interleukin-6: evidence for a unique autocrine signaling mechanism. J Biol Chem. 2004;279(50):51793–803. Epub 2004/07/20.
302. Chen D, Choi YB, Sandford G, Nicholas J. Determinants of secretion and intracellular localization of human herpesvirus 8 interleukin-6. J Virol. 2009;83(13):6874–82. Epub 2009/04/24.
303. Cousins E, Nicholas J. Role of human herpesvirus 8 interleukin-6-activated gp130 signal transducer in primary effusion lymphoma cell growth and viability. J Virol. 2013;87(19): 10816–27. Epub 2013/08/02.
304. Xiang Y, Ma N, Wang D, Zhang Y, Zhou J, Wu G, et al. MiR-152 and miR-185 co-contribute to ovarian cancer cells cisplatin sensitivity by targeting DNMT1 directly: a novel epigenetic therapy independent of decitabine. Oncogene. 2014;33(3):378–86. Epub 2013/01/16.
305. Cohen T, Nahari D, Cerem LW, Neufeld G, Levi BZ. Interleukin 6 induces the expression of vascular endothelial growth factor. J Biol Chem. 1996;271(2):736–41.
306. Aoki Y, Jaffe ES, Chang Y, Jones K, Teruya-Feldstein J, Moore PS, et al. Angiogenesis and hematopoiesis induced by Kaposi's sarcoma-associated herpesvirus-encoded interleukin-6. Blood. 1999;93(12):4034–43.
307. Vart RJ, Nikitenko LL, Lagos D, Trotter MW, Cannon M, Bourboulia D, et al. Kaposi's sarcoma-associated herpesvirus-encoded interleukin-6 and G-protein-coupled receptor regulate angiopoietin-2 expression in lymphatic endothelial cells. Cancer Res. 2007;67(9): 4042–51.
308. Suthaus J, Stuhlmann-Laeisz C, Tompkins VS, Rosean TR, Klapper W, Tosato G, et al. HHV-8-encoded viral IL-6 collaborates with mouse IL-6 in the development of multicentric Castleman disease in mice. Blood. 2012;119(22):5173–81. Epub 2012/04/12.