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Molecular Biology of KSHV in Relation to HIV/AIDS-Associated Oncogenesis

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2.1. Introduction

Discovered in 1994, KSHV is a human oncogenic gammaherpesvirus [1]. KSHV is causatively associated with several malignancies, including Kaposi's sarcoma (KS), primary effusion lymphoma (PEL), multicentric Castleman's disease (MCD), and KSHV inflammatory cytokine syndrome (KICS), most of which are commonly found in HIV-1-infected individuals [1, 2, 3, 4].

KS is a multifocal mesenchymal neoplasm characterized by neo-angiogenesis, inflammatory infiltration, and spindle-shaped tumor cells that express mixed cellular markers, including vascular and lymphatic endothelial, mesenchymal, and hematopoietic precursor cells [5]. Early stage of KS primarily affects mucocutaneous tissues but advanced stage of KS is often involved with visceral organs [5]. KS is one of the most common malignancies in AIDS patients. While the advent of antiretroviral therapy has substantially reduced the incidence of KS in Western countries, it has stabilized or even rebound in recent years in some populations, and continues to be the most common cancer in some African regions [6]. Hence, KS remains to be one of the most important malignancies in AIDS patients causing significant morbidity and mortality.

PEL is a rare and aggressive non-Hodgkin's B cell lymphoma clinically characterized by lymphomatous effusions in body cavities usually without tumor masses [7]. PEL often occurs in advanced AIDS patients with a decreased CD4 T cell count at diagnosis. Approximately, half of PEL patients have KS or are at risk for developing KS. PEL is resistant to conventional chemotherapy with a short median survival of less than 6 months [7].

MCD is a polyclonal B cell lymphoproliferative disorder characterized by inflammatory symptoms, including fever, cachexia, lymphadenopathy, splenomegaly, cytopenia, and hypoalbuminemia [8]. MCD in the setting of HIV is typically associated with KSHV infection and is usually fatal without treatment. Furthermore, there is no established standard of treatment for KSHV-associated MCD [8].

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KICS is a newly described severe systemic inflammatory symptom associated with elevated viral loads and cytokine production [4]. The symptoms of KICS are similar to MCD but without any pathological evidence of MCD. KICS patients have poor prognosis, stressing the need for better understanding of its biology [9].

To dissect the biology of KSHV-associated malignancies and discover new approaches for potential therapy, extensive studies of KSHV from the aspects of virology to its associated pathogenesis have been done in the last three decades. Here, we present an update of literature review of KSHV in the following topics: (1) primary infection, (2) life cycle, (3) immunity, (4) tumorigenesis, (5) inflammation, and (6) metabolism. Because of space constraint, we can't describe all studies in detail and cite every reference. However, several excellent reviews have been published in the last few years and readers are advised to refer to those articles and the previous edition of this book chapter for additional information [5].

2.2. KSHV Primary Infection

KSHV has a broad cellular tropism and infects numerous cell types in vivo and in vitro, including endothelial cells, B cells, monocytes, macrophages, epithelial cells, keratinocytes, mesenchymal stem cells, and neurons [10, 11, 12, 13, 14]. Following primary infection, KSHV eventually establishes latency in all the cell types examined so far. While KSHV establishes latent infection without any active lytic replication in some cell types, it has an early full productive replication phase shortly after primary infection in others [15, 16]. To better understand the mechanism that controls KSHV latency and lytic replication following primary infection, it is necessary to identify cell types and conditions that support early lytic replication and the associated cellular pathways.

2.2.1. Attachment, Entry, and Cellular Receptors

KSHV enters the host cell and delivers its genome into the nucleus through a series of events tightly regulated by diverse viral and host factors [17, 18]. These events include attachment to the host cell surface, binding to specific entry receptors, and internalization through fusion of viral envelope with the membrane of intracellular vesicles following receptor-mediated endocytosis [17, 18].

The attachment of KSHV to the host cell is through interactions between viral glycoproteins (gB, gH, and gpK8.1) and cell surface molecule heparan sulfate, a linear polysaccharide ubiquitously expressed at the extracellular matrix [19, 20, 21, 22]. Following attachment, KSHV binds to the specific entry receptors, including integrins, DC-SIGN, xCT, and ephrin type-A receptor 2 (EphA2), and activates a cascade of signaling pathways to promote receptor-mediated endocytosis [17, 18].

Integrins are a large family of cell adhesion receptors, widely expressed in various cell types, including endothelial cells and B cells. KSHV was the first herpesvirus demonstrated to utilize integrins as entry receptors [13]. An integrin binding RGD motif (arginine–glycine–aspartic acid) of glycoprotein gB mediates its interactions with integrins α3β1, αVβ3, and αVβ5 expressed on the surface of human foreskin fibroblasts (HFF), human dermal

microvascular endothelial cells (DMVEC), human monocytic THP-1 cells, human fibrosarcoma HT1080, Vero cells, and HEK-293T cells [13, 23, 24, 25].

Dendritic cell-specific intercellular adhesion molecule-3-grabbing non-integrin (DC-SIGN) is a C-type lectin expressed by dendritic cells (DCs), macrophage subpopulations, and activated B lymphocytes. KSHV uses DC-SIGN as a binding and entry receptor to infect human myeloid DCs, macrophages, and activated B cells [26, 27]. While blocking binding of KSHV to DC-SIGN does not affect virus attachment to the cells, it inhibits KSHV infection in human monocytic THP-1 cells [23].

Human cysteine/glutamate exchange transporter system x_c^- (xCT) is an amino acid transporter that imports L-cystine and exports L-glutamate across plasma membrane [28]. xCT mediates KSHV cell fusion and virion entry [29]. xCT interacts with α3β1 integrin to form a complex, which triggers downstream signaling cascades essential for viral gene expression during primary infection of DMVEC [24].

Eph2A, a receptor protein tyrosine kinase (RTK), serves as an entry receptor through direct interaction with gH/gL glycoprotein complex [12, 30]. Eph2A plays an important role in regulating macropinocytosis and trafficking of KSHV through its association with signaling molecules (e.g., FAK, Src, and c-Cbl) in the lipid raft (LR) regions during primary infection of DMVEC [31]. In contrast, KSHV infection of HFF induces association of integrins with Eph2A in non-LR regions, suggesting a crucial role of Eph2A in KSHV entry through clathrin-mediated endocytosis [32].

2.2.2. Internalization and Intracellular Trafficking

KSHV infects most types of cells through clathrin-mediated endocytosis and macropinocytosis. Clathrin-mediated endocytosis is an endocytic portal into cells through which cargos are taken up using clathrin-coated vesicles. KSHV enters human umbilical vein endothelial cells (HUVEC), HFF, HEK293 cells, and BJAB cells via clathrin-mediated endocytosis [33, 34, 35]. During infection of HUVEC, KSHV particles are co-localized with early endosome antigen (EEA1) and late endosome/lysosome marker (LAMP1) [34]. By electron microscopy, KSHV virions are present in the endocytic vesicles in HFF cells [33], and KSHV entry is sensitive to inhibitors of clathrin-mediated endocytosis [33, 34].

KSHV utilizes macropinocytosis as the major route to enter DMVEC [36]. Inhibition of membrane blebbing, an important event in macropinocytosis, significantly blocks KSHV entry [37]. It is identified that ESCRT-0 component Hrs regulates KSHV entry and ESCRT-I protein Tsg101 plays a role in the trafficking of virus particles in DMVEC [38, 39].

Studies on other cell types further suggest that KSHV entry is cell type-dependent. KSHV enters THP-1 via clathrin- and caveolae-mediated endocytosis but not macropinocytosis [23] while KSHV enters primary B lymphocytes by DC-SIGN-mediated endocytosis [26].

Upon internalization, the intracellular transport of KSHV particles relies on the cytoskeletons. In HUVEC, KSHV is co-localized with actin filaments during early infection and induces dynamic actin cytoskeleton rearrangements. Disruption of actin dynamics significantly inhibits KSHV trafficking [34]. In addition, KSHV infection modulates

microtubule polymerization to promote the trafficking of viral capsids in HFF [40]. Disruption of microtubule formation or impairing dynein-directed retrograde microtubule transport strongly reduces KSHV trafficking [40].

2.2.3. Regulation of Cellular Signaling Pathways During Primary Infection

KSHV dysregulates multiple signaling pathways to promote primary infection [18]. Interactions between KSHV and cell surface receptors activate focal adhesion kinase (FAK) signaling in several cell types [41]. Activated FAK is vital for many processes including cytoskeleton rearrangement and endocytosis, which facilitate virus entry [42]. Calcium and integrin binding protein 1 (CIB1), an enhancer of FAK, ERK1/2, and PAK kinases [43, 44], facilitates Eph2A-related signaling and regulates KSHV entry and macropinocytosis [45]. c-Cbl, a multifunctional E3 ubiquitin ligase, is induced by KSHV to promote virus entry in endothelial cells [37, 46, 47]. In addition, KSHV infection induces reactive oxygen species (ROS) to promote virus entry and subsequent viral gene expression [48].

Primary KSHV infection activates ERK, JNK, p38 MAPK pathways to promote virus entry, viral gene expression, and productive viral replication [49, 50, 51]. KSHV infection suppresses dual-specificity phosphatase-1 (DUSP1) to activate MAPK signaling, facilitating viral gene expression, pro-inflammatory factor secretion, and cell invasiveness [52]. In HUVEC, KSHV activates MSK/CREB1 signaling pathway in an ERK- and p38-dependent manner to regulate viral lytic replication at the postentry stage [53]. Endogenous activity of AMPK, which maintains cellular homeostasis, inhibits KSHV lytic replication [54]. Activation of AMPK activity decreases while inhibition of AMPK increases KSHV lytic replication during primary infection of HUVEC [54]. In addition, KSHV infection leads to sustained NF-κB induction, which regulates viral and host cell gene expression and possibly affects the establishment of latent infection [55]. Nuclear factor erythroid 2-related factor 2 (Nrf2) is activated by KSHV infection through an ROS-dependent pathway [56]. Knockdown of Nrf2 decreases early lytic gene expression but increases latency-associated nuclear antigen (LANA) expression in the infected cells, indicating its crucial role in viral gene expression [56].

2.2.4. Viral Gene Expression During Primary Infection and the Establishment of Viral Latency

Viral gene expression profiles during KSHV primary infection are heavily dependent on the types of cells infected [57, 58, 59]. In cells that support productive KSHV infection (e.g., HUVEC), the expression of latent transcripts precedes the cascade of lytic genes [57]. Latent transcripts are sustained at high levels throughout infection. The lytic transcripts are expressed in the order of immediate early (IE), early (E), and late (L) transcripts, and reach peaks at around 54 h post infection (hpi). After 54 hpi, the levels of lytic transcripts decline while latent transcripts continue to increase, leading to the switch from lytic replication to viral latency [57]. In cells such as CD14+ monocytes, HFF, and DMVEC that support minimal lytic activities without producing infectious virions during KSHV primary infection, the expression of lytic transcripts is weak and transient (within 24 hpi) while latent transcripts are expressed throughout the infection process [58, 59].

The establishment of latency is an essential step for persistent infection and induction of KSHV-associated malignancies. One hallmark of KSHV latency is the global repression of viral lytic genes. During primary infection, the chromatin-free KSHV genome undergoes biphasic chromatinization with an initial transcriptionally active euchromatin phase characterized by high levels of the H3K4me3 and H3K27ac activating histone marks, followed by a heterochromatinization phase featured by decreased levels of activating histone marks and increased levels of repressive marks H3K27me3 and H2AK119ub [60, 61, 62]. The euchromatin-to-heterochromatin transition corresponds with the expression switch of viral lytic to latent genes and depends on the recruitment of polycomb repressive complexes 1 and 2 (PRC1 and PRC2) to lytic promoters by LANA [63].

KSHV triggers DNA damage response (DDR) signaling inducing phosphorylation of DDR-associated proteins, ataxia telangiectasia mutated (ATM) and H2AX, during primary infection of endothelial cells [64]. Inhibition of ATM or H2AX activation leads to over 80% reduction in the nuclear viral DNA copy number, indicating an essential role of the DDR proteins for the establishment of KSHV latency during primary infection [64].

2.3. KSHV Life Cycle

Following an acute phase of infection with or without active lytic replication, KSHV enters latency, which is essential for the development of KSHV-associated malignancies [65]. Upon stimulation by specific intracellular and extracellular signals, latent KSHV is reactivated into lytic replication which culminates in virion production and cell death [65].

2.3.1. The Latency Locus

The KSHV latency locus encodes LANA, viral homologues of the cellular FLICE-like inhibitory protein (vFLIP) and cyclin D (vCyclin), Kaposin A, B, and C, and 12 precursor microRNAs (pre-miRNAs). Transcription of the latent locus occurs from LANA promoters (LT1 and LT2) and Kaposin promoter. LT1 drives the expression of LANA, vCyclin, and vFLIP whereas LT2 drives the expression of vCyclin and vFLIP [66, 67, 68]. The LANA promoter is bidirectional and can drive the expression of upstream lytic genes such as surface glycoprotein vOX2 and viral G-protein coupling receptor (vGPCR) during reactivation [69]. Of the 12 pre-miRNAs, miR-K1 to -K9 and -K11 form a cluster region located between vFLIP and Kaposin while miR-K10 and miR-K12 are in the Kaposin coding region or 3’UTR, respectively [70]. In addition to the latency locus, KSHV encodes another latent protein viral interferon regulatory factor 3 (vIRF-3) located outside the latency locus, which is expressed in PEL but not in KS cells [71].

2.3.2. KSHV Latency and Latent Nuclear Antigen (LNA) or Latency-Associated Nuclear Antigen (LANA)

LANA (LNA) is a KSHV latent protein discovered as an immunodominant antigen and has been used for detecting KSHV infection [72, 73, 74]. LANA is approximately 1162aa in length with a proline-rich N terminal and repeats regions (CRs) composed of glutamine (Q), glutamic acid (E), and aspartic acid (D) [75]. The CRs can be further divided into three distinct regions: CR1 (aa 321–429), CR2 (aa 430–768), and CR3 (aa 769–937), with CR3

containing a leucine zipper domain. CR1 is involved in immune evasion by inhibiting major histocompatibility complex class I (MHC-I) peptide presentation in *cis* [76] while CR2 and CR3 decrease LANA synthesis and enhance its stability [77]. Although its predicted size is 135 kDa, LANA is resolved as double bands of 226–234 kDa in SDS-PAGE [72]. The second band is the result of a 76 aa truncation in the C-terminal region [78]. Besides the two bands, multiple bands between 150 and 180 kDa are present in KSHV-infected cells due to noncanonical translation initiation [79].

LANA is a multifunctional protein and its key function is to maintain the cellular persistence of KSHV episome [65]. During latency, the KSHV genome replicates once in each cell cycle, and the copy number is stable (40–150 copies/cell in PEL cells) [80, 81, 82]. Without LANA, KSHV is unable to establish and maintain its episome in mammalian cells [83]. LANA has an essential nuclear localization signal (NLS) at its N-terminus (aa 24–30) and a second one at the C-terminus, and is detected in dot-like pattern by immunohistochemistry or immunofluorescence [73, 74, 84]. The N-terminus also has a chromosome binding site (CBS) (aa 5–13), which interacts with histones H2A/H2B whereas the C-termini has a DNA binding and a dimerization domain (DBD), which allows LANA to bind to LANA-binding sites (LBS) located within KSHV terminal repeat (TR) region [85, 86, 87, 88].

LANA interacts with chromatin-associated proteins such as heterochromatin protein 1α (HP1), KSHV LANA-interacting protein 1 (KLIP1), methyl CpG-binding protein (MeCP2), bromodomain protein 4 (Brd4), RING3/Brd2, kinetochores-associated proteins as centromere protein F (CENP-F), budding uninhibited by benzimidazoles (Bub-1), and nuclear mitotic apparatus protein (NuMA) [89, 90, 91, 92, 93, 94]. Furthermore, LANA is associated with nucleophosmin (NPM), and the origin recognition complexes (ORCs) [95]. Some of these interactions are essential for KSHV genome segregation to daughter cells and repression of KSHV lytic replication. LANA silences the replication and transcriptional activator (RTA) promoter and interacts with RTA to inhibit its transactivation function [96]. Deletion or disruption of LANA abolishes the establishment of KSHV latency and increases the expression of KSHV lytic genes and production of infectious virions [83, 97]. Hence, LANA is the predominant regulator in maintaining latency by mediating episome replication, proper segregation to daughter cells, and repressing KSHV lytic replication program [65]. LANA also contributes to KSHV latency by promoting host cell proliferation and survival, which will be detailed in a later section.

2.3.3. Epigenetic Silencing and Regulation of KSHV Latency

To silence the expression of viral lytic genes, the KSHV genome undergoes epigenetic remodeling during latency. The KSHV genome is heavily methylated and contains histone repressive marks and HDACs [61, 62, 98, 99, 100, 101, 102]. To mediate viral genome replication, LANA binds to the latent origin of replication in the TR, which also harbor ORC, MCM, CDC6, PARP1, and hyperacetylated histones [100, 103, 104, 105]. During latency, the spread of transcription beyond the latent locus is arrested by H19/Lgf2 insulators recruited to the CTCF-binding site, which also harbors CTCF, cohesins, RAD21, SMC1 and SMC 3 [106, 107], mediating viral chromosome conformation, expression of latent genes, and silencing of lytic genes [108, 109, 110]. In addition to LANA, vFLIP and miR-K1

promote KSHV latency by activating the NF-κB pathway [111, 112]. Several KSHV miRNAs inhibit RTA expression by direct targeting and silencing or indirect activation of cellular pathways including Rbl2, DNMTs, NFIB, and IKKε [113, 114, 115, 116, 117]. These cellular factors could cause chromatin remodeling of KSHV genome. KSHV miRNAs also target several other viral genes, which could regulate viral latency [118].

2.3.4. Reactivation of KSHV from Latency

The mechanism of KSHV reactivation is involved with complex interactions of viral genes, cellular factors, and extracellular signals. During reactivation, the quiescent state of the KSHV genome is disrupted and undergoes epigenetic remodeling, resulting in the expression of viral lytic genes and production of infectious viral particles [119].

2.3.5. Viral Genes Required for Reactivation

KSHV lytic genes can be broadly divided into three classes: IE, E, and L genes. IE gene expression is not dependent on de novo translation of any proteins, whereas E and L genes require de novo expression of proteins. Late genes are also dependent on viral DNA replication. Here, we will discuss several viral lytic genes that are important for viral lytic replication.

RTA is an IE gene. Expression of RTA is essential and sufficient for KSHV reactivation [120, 121]. RTA transactivates numerous viral genes, including itself, by binding to the palindromic RTA-responsive element (RRE) [122, 123, 124, 125, 126]. RTA cooperates with cellular factors such as Sp1, Oct-1, XBP-1, RBP-Jk, and C/EBPα to transactivate genes [127, 128, 129, 130, 131]. As an E3 ubiquitin ligase, RTA targets numerous repressors of viral lytic replication for degradation [132, 133, 134, 135]. RTA binding to origin of lytic replication (oriLyts) is required for viral DNA replication [136, 137]. Several isoforms of RTA, which possess transactivation activities weaker than the canonical isoform, have been identified but the regulation of their expression as well as their specific target genes remain unclear [138]. Hence, RTA's complex functions are not fully understood despite it is known as the master regulator of KSHV lytic replication.

mRNA transcript accumulation (MTA) is an E gene required for KSHV reactivation [139, 140]. MTA interacts with RTA to enhance RTA expression [141]. Importantly, MTA mediates viral transcript processing by hijacking splicing and nuclear export factors such as TREX for efficient viral gene expression, particularly for intronless viral transcripts [142]. However, MTA's role in nuclear export is controversial [143]. MTA interacts with an RNA stem-loop structure termed the MTA-responsive elemen (MRE) [144, 145]. Of interest, MTA protects vIL6 from miRNA-mediated degradation though the exact mechanism remains unknown [146]. To promote translation, MTA interacts with PYM to shuttle transcripts to the 48S transcription pre-initiation complex [147]. Taken together, MTA enhances viral gene expression by hijacking cellular RNA processing events and translation.

K-bZip encoded by ORF-K8 is an E gene. K-bZip is a leucine zipper protein with multiple functions [148]. It interacts with RTA and inhibits RTA transactivation of several viral genes, notably ORF57, ORF-K15, itself, and RTA autoactivation [149]. K-bZIP interacts with HDAC1/2 to silence viral promoters [150] and this repressive function depends on its

SUMO modification of KSHV genome and heterochromatin histone demethylase JMJD2 [151, 152, 153, 154]. K-bZIP supports lytic DNA replication by overcoming LANA's repression of the OriLyts [136, 155]. Furthermore, viral protein kinase (vPK/ORF36) co-localizes with K-bZIP at oriLyts and phosphorylates K-bZIP to prevent its sumoylation, thus reducing its transcription repression activity [156]. Taken together, K-bZIP contributes to viral DNA replication and repression of lytic genes during lytic replication.

2.3.6. Factors Involved in KSHV Reactivation

KSHV reactivation from latency is accompanied by dynamic chromatin remodeling [101, 102]. Inhibition of class II HDACs, EZH2, or DNA methylation with small molecules is sufficient to induce KSHV reactivation [101, 102, 157]. During reactivation, the KSHV episome gains activating histone marks (H3K4me3, acH3) and loses repressive histone marks (H3K9me3, H3K27me3, H4K20me3) [157]. This is facilitated by RTA, which recruits CBP/p300 and SWI/SNF to promote H3K27Ac on lytic promoters [158]. Inhibition of SIRT1, a class III HDAC and NAD^+ sensor, results in expression of lytic genes thus linking epigenetics to the cellular metabolic state [98, 99]. In fact, high glucose suppresses SIRT1 leading to KSHV reactivation [159].

KSHV infection often occurs in the context of immunosuppression [160]. How KSHV interacts with other pathogens is poorly understood in vivo but several in vitro studies have attempted to delineate these events. HIV Tat alone can induce RTA expression and enhance KSHV entry into endothelial cells [161, 162, 163]. Coinfection of PEL cells with EBV favors viral persistence of both viruses [164, 165]. KSHV RTA, EBV ZTA, and EBV LMP1 prevent reactivation of both viruses. Additionally, HCMV, HHV-6, HSV-1, HSV-2, and HHV-7 can induce KSHV reactivation [166, 167, 168, 169, 170, 171]. Bacterial metabolic products such as LPS, short-chain fatty acids, and lipoteichoic acid enhance infectivity and reactivation [172, 173, 174].

Hypoxia plays a critical role in reactivation [175]. Binding of HIF-1α to hypoxia-responsive elements (HRE) in the promoters of KSHV lytic genes enhances their expression and lytic replication [175, 176, 177]. Furthermore, LANA cooperates with HIF-1α at the HRE to enhance RTA expression [178, 179]. Another hypoxia-inducible gene, XBP-1, binds to the RTA promoter to enhance reactivation [180, 181]. Cross talk between hypoxia and epigenetics could occur through KAP1, which is recruited to the KSHV genome through LANA, and decreased levels of KAP1 during hypoxia enhance lytic gene expression [182, 183].

Moreover, oxidative stress also contributes to KSHV reactivation. In fact, hydrogen peroxide (H_2O_2) is necessary and sufficient for inducing KSHV reactivation [184]. Since KS is a highly inflammatory tumor, the abundant infiltrating immune cells and inflammatory cytokines in KS tumors could secrete or induce H_2O_2, respectively, leading to KSHV reactivation [184, 185]. H_2O_2 activates MAPK leading to phosphorylation of ERK1, JNK, p38, and c-Jun, which is sufficient for KSHV reactivation and this can be reversed by the antioxidant N-acetyl-cysteine (NAC) [184, 185]. Furthermore, ROS induced by anticancer drugs such as cisplatin and arsenic trioxide reactivate KSHV and cause cell death in PEL cells [185].

2.4. KSHV and Immunity

While the immune system is dedicated to protecting the host from invading pathogens such as viruses, KSHV has evolved various strategies to counteract both the innate and adaptive immune responses, which are essential for viral replication and persistent infection.

2.4.1. KSHV and Innate Immunity

Several KSHV-encoded proteins interfere with both type I (IFN-α and IFN-β) and type II (IFN-γ) interferon responses. KSHV was the first virus found to encode viral homologs of cellular interferon regulatory factors (vIRFs) [186]. Each of the four vIRFs blocks the IRF-mediated transcription of type I IFN by a distinct mechanism [186, 187, 188]. Moreover, ORF45 and RTA inhibit IRF7-dependent type I IFN response [189, 190] while K8 inhibits IRF3-mediated IFN-β transcription [191]. ORF-K3 and ORF-K5, which are viral E3 ligases, repress the IFN-γ-mediated JAK/STAT signaling pathway by inducing the degradation of IFN-γ [192,193].

The pattern recognition receptors (PRRs) sense various pathogen-associated molecular patterns (PAMPs) and trigger the type I IFN signaling and production of inflammatory cytokines during pathogen infection. KSHV stimulates TLR3 expression at the early stages of de novo infection; however, the expression of vIRFs inhibits TLR3-mediated immune responses at later time points [194, 195, 196]. RTA, ORF21, and ORF31 inhibit both TLR2 and TLR4 signaling [194, 197]. In addition to modulating the TLR signaling pathway, KSHV ORF63 blocks the cellular NOD-like receptor (NLR)-mediated pathway whereas ORF64 inhibits the activation of retinoic acid-inducible gene-I (RIG-I) [198]. KSHV DNA is sensed by IFI16 and cGAS-STING pathways leading to the activation of inflammasome [199, 200, 201, 202]. To ensure efficient viral lytic replication, KSHV encodes numerous proteins including vIRF1, ORF52, and LANA to inhibit the cGAS-STING pathway [199, 200, 201], while KSHV lytic replication leads to the degradation of IFI16 though the mechanism remains unclear [203].

To facilitate viral evasion of cytotoxic reaction, KSHV induces a Th2-polarized rather than a Th1-polarized response. Three KSHV-encoded CC-chemokine ligands (vCCL), the homologs of cellular chemokines, compete with cellular chemokines to prevent activation of chemokine receptors [188]. KSHV complement control protein (KCP/ORF4) is a functional homolog of the complement regulatory protein which inhibits the activation of the complement system [204]. This mechanism is likely to protect both KSHV-infected cells and free virions from complement-mediated neutralization during acute viral infection. In contrast, KSHV activates the alternative complement system by downregulating the complement regulatory proteins CD55 and CD59 during latency, which is essential for cell survival and persistent infection [205].

KSHV has evolved strategies to evade the natural killer (NK) cells. ORF-K5 decreases cell surface expression of NK-activating ligands including MICA, MICB, and AICL as well as the costimulatory molecules ICAM and B7.2 [188, 206]. Similarly, miR-K12-7 targets MICB mRNA [207] while ORF54 decreases the expression of another NK ligand, NKp44L [208].

2.4.2. KSHV and Adaptive Immunity

Both KS patients and asymptomatic individuals develop T cell responses against several KSHV lytic and latent proteins [209]. Importantly, reconstitution of the immune system through antiretroviral therapy can lead to KS tumor regression [210]. suggesting an important role of the KSHV-specific T cell response, particularly the CD8+ T cell response, in the development of KSHV-associated malignancies [209]. KSHV also induces strong humoral responses as antibodies against various viral antigens are present in KS and KSHV-infected patients [72, 73, 74, 211, 212].

B cell activation and differentiation into antibody-producing plasma cells or memory B cells are critical aspects of the adaptive immune response. Several studies suggest that KSHV targets both aspects of the B cell biology to evade the humoral immune response. ORF-K1 reduces the expression of bone marrow stromal antigen 2 (BST-2), which is constitutively expressed in mature B cells [192]. and downregulates B cell receptor on the cell surface [213] while ORF-K15 blocks BCR transduction signal, contributing to decreased B cell activation [213].

Evading the cell-mediated immune response is an important strategy for KSHV persistent infection. ORF-K3 and -K5 enhance the internalization and lysosomal degradation of MHC-I molecules through ubiquitination of the cytosolic tails [214, 215, 216, 217]. vIRF1 and vFLIP mediate MHC-I downregulation [218]. LANA evades immune surveillance by inhibiting MHC class I peptide presentation [76]. KSHV induces cellular suppressor of cytokine signaling 3 (SOCS3), and together with vIRF3, interferes with MHC class II antigen presentation to evade KSHV-specific CD4+ T helper cell immune response [219, 220]. Besides impairing antigen presentation, KSHV interferes with the function of antigen presenting cells by inhibiting differentiation of monocytes into dendritic cells [221] and downregulating costimulatory molecules required for efficient activation of CD8+ T cells [214, 222].

2.5. KSHV and Tumorigenesis

In KS tumors, most of the tumor cells are latently infected by KSHV, suggesting the importance of latent infection and latent genes in the development of KS tumors [65]. A small number of tumor cells undergo spontaneous lytic replication in early stage of tumors, which is essential for the spread and progression of this stage of tumors. However, there is no lytic cell in late stage of KS tumors [65]. Spontaneous lytic replication is also present in small number of cells in PEL and MCD [65]. Numerous KSHV latent and lytic genes have been shown to have oncogenic and tumor-promoting functions [188]. The recent development of a model of KSHV-induced cellular transformation and tumorigenesis of primary cells has allowed the delineation of the cellular pathways and viral genes that promote tumorigenesis in the context of viral infection [14].

2.5.1. Models of KSHV-Induced Cellular Transformation and Tumorigenesis

The origin of KS tumor cells remains controversial. KSHV infects both vascular and lymphatic endothelial cells and reprograms them to acquire KS-like cell surface markers

[223, 224]. KSHV efficiently infects endothelial cells and prolongs their life span but cellular transformation remains elusive [225, 226]. Transfection of mouse bone marrow endothelial-lineage cells with recombinant KSHV BAC36 genomes results in immortalization of a subset of cells, which induces tumors in nude mice [227]. However, the exact target cells are unclear and the efficiency is low. In contrast, KSHV efficiently infects and transforms primary rat embryonic metanephric mesenchymal precursor (MM) cells [14]. KSHV-transformed MM cells (KMM) lose contact inhibition and form colonies in soft agar. KMM cells efficiently induce tumors in nude mice with virological and pathological features reminiscent of KS [14]. While KSHV can also infect and transform human mesenchymal stem cells of diverse origins, the efficiency of cellular transformation is much lower [228]. KSHV infection of rat and human mesenchymal stem cells reprograms them to acquire KS-like phenotypes including cell surface markers, and enhances their angiogenic, invasive, and transforming phenotypes [14, 228, 229].

2.5.2. KSHV Viral Genes and Tumorigenesis

The roles of the KSHV latent genes LANA, vFLIP and vCyclin, and miRNAs in tumorigenesis have been extensively studied. LANA promotes cell proliferation and survival by inhibiting tumor suppressor genes p53, p73, pRb, and TGF-β signaling [230, 231, 232, 233], and activating c-Myc, emmprin, and survivin [234, 235, 236, 237]. LANA promotes tumorigenesis by upregulating BMP-p-Smad1-Id1 pathway in KMM cells [238]. LANA upregulates Par3, SNAIL, and MMP9 while downregulates E-cadherin to promote cell proliferation in B cells [239]. KSHV-encoded miRNAs and vFLIP activate the NF-κB pathway and are essential for KSHV-induced cellular transformation and tumorigenesis by regulating cell proliferation, survival, homeostasis, and metabolic pathways [240, 241, 242]. vCyclin alone can interact with numerous CDKs to promote cell cycle progression and tumorigenesis, and antagonizes the senescence/G1 arrest response triggered by NF-κB hyperactivation [243, 244, 245, 246]. In the context of KSHV infection, vCyclin only promotes cellular transformation and tumorigenesis by overriding cell contact inhibition [247].

Numerous KSHV lytic genes possess cellular transforming and growth-promoting activities. vIRF1 is the first KSHV oncogene identified [186]. It targets interferon, p53, and TGF–β pathways [186, 248, 249]. vGPCR is unique in that it is constitutive active without the need of a ligand. It has robust oncogenic activity [250]. vGPCR transgenic mice develop KS-like lesions [251]. Mechanistically, vGPCR activates Akt and mTOR pathways, and promotes genomic instability through miR-34a [252, 253, 254]. Unlike human IL-6, vIL6 only signals through gp130 to activate several downstream pathways, such as JAK/STAT, MAPK, and Akt, driving cellular proliferation, inflammation, and apoptosis inhibition [255, 256]. Of interest, vIL6 can induce intracellular signaling and interacts with splice variant 2 of vitamin K epoxide reductase complex subunit 1 (VKORC1) to promote PEL cell proliferation and survival [257, 258]. ORF-K1 also possesses oncogenic activity [259]. It activates Akt and AMPK pathway to promote cell proliferation and survival [260, 261]. Whether KSHV lytic genes contribute to KSHV-induced tumorigenesis remains to be tested in the context of viral infection.

2.5.3. Cellular Genes/Pathways in KSHV-Associated Malignancies

Extensive studies have identified cellular genes/pathways required for KSHV-associated malignancies. Transcriptional factors, such as c-Myc and STAT3, are required for cell survival, and the inhibition of c-Myc and STAT3 induced apoptosis in PEL cells [262, 263]. Epigenetic factors, including class I and II HDACs, as well as class III HDAC SIRT1 are essential for cell proliferation and survival in PEL cells, and their inhibitors SAHA and tennovin-6 significantly induced cell cycle arrest and apoptosis in vitro and in vivo [264, 265, 266]. In addition to the NF-κB and BMP-Smad1-Id pathways that are essential for cell proliferation and cellular transformation [238, 240, 241, 242], Akt and mTOR are also essential for cell proliferation in KS cells [267] while hepatocyte growth factor (HGF)/c-MET pathway is essential for cell cycle progression and cell survival in PEL cells [268, 269].

2.6. KSHV and Inflammation

2.6.1. Kaposi's Sarcoma: A Tumor Associated with Inflammation

Inflammation can have a double role in the development of cancer. Acute inflammatory response is considered as a physiological process required for the control of microbial infections and tumor growth. However, by stimulating cell proliferation and inhibiting apoptosis, chronic inflammation becomes a pathologic process participating in the modifications of the microenvironment, enhancing uncontrolled tissue regeneration, angiogenesis, and tumorigenesis [270]. It is estimated that more than 25% of cancers are associated with inflammation [271].

Chronic inflammation, a hallmark of KSHV-associated malignancies, participates KS progression through the complex interplay between viral and cellular factors. By interfering with the intracellular signaling pathways during lytic and latent phases of infection, KSHV induces an inflammatory neoplastic network in the tumor microenvironment, which is mainly associated with the abnormal lympho-endothelial proliferations and the recruitment of activated myeloid and lymphoid immune cells [272]. Indeed, at the early stage of tumors, the KS microenvironment has a high level of pro- and anti-inflammatory cytokines (IL-6, TNF-α, and IL-10, respectively), chemokines (CXCL12, CXCR4, CXCR7), interferon (IFN-γ), as well as growth factors (VEGF) [273, 274, 275]. These cytokines can be released by different cell types including monocytes, endothelial cells, and KS tumors. During tumor growth, these mediators stimulate resting and non-proliferative lympho-endothelial cells to enhance inflammation, and therefore promote angiogenesis [276, 277].

2.6.2. Latent Viral Factors Involved in Inflammation

LANA upregulates emmprin expression, which induces the secretion of IL-6, VEGF, and MMPs, and enhances inflammation and angiogenesis [236, 278]. By stabilizing the Notch effector Hey-1, LANA also represses the expression of Prox-1 to modulate the differentiation of lymphatic endothelial cells [279]. Moreover, LANA activation of the Notch pathway enhances the invasiveness of KS tumors by activating PDGFRβ [280]. As stated in the previous section, LANA participates in the suppression of specific T cells immune response by inhibiting MHC-I antigen presentation through its acidic central repeat

domain [281], and by downregulating MHC-II gene expression on APCs through the interaction with RFX proteins to inhibit the recruitment of CIITA to the MHC-II promoter [282].

vFLIP activates the classical and alternative NF-κB signaling pathways and participates in the upregulation of pro-inflammatory cytokines [283, 284]. Particularly, vFLIP promotes tumorigenesis through the induction of COX-2 and its inflammatory metabolite PGE2 in an NF-κB-dependent manner [283, 285].

Most of the KSHV-encoded miRNAs are expressed during latency and play significant roles in tumor growth, inflammation, and angiogenesis. Numerous KSHV miRNAs induce inflammation by activating the NF-κB pathway [112, 242]. Ectopic expression of the miRNA cluster in endothelial cells induces the expression of pro-inflammatory and pro-angiogenic cytokines MMP1, MMP13, and VEGFA [286]. VEGF is important for the recruitment of stem cells and macrophages at the site of infection, and therefore participates in the inflammatory microenvironment of KS tumors [287]. By inducing CXCR2 and activating Akt signaling pathway through targeting GRK2 stimulation, miR-K3 promotes angiogenesis, migration, and invasion of endothelial cells [288, 289]. The miRNAs derived from miR-K6, miR-K6-3p, and miR-K6-5p promote cell migration, invasion, and angiogenesis by targeting SH3BGR to activate the STAT3 pathway and CD8 to activate the c-Met pathway, respectively [290, 291]. miR-K12 promotes cell survival and proliferation by targeting the angiogenesis inhibitor THBS1 and SMAD5 to downregulate TGF-β signaling [292, 293].

In the context of inflammation, Kaposin B participates in the lymphatic reprogramming of vascular endothelial cells [294]. Kaposin B activates the p38/MK2 pathway leading to the stabilization of targeted gene transcripts including pro-inflammatory cytokines IL-6 and GM-CSF, as well as the lympho-endothelial differentiation factor PROX1 [294, 295]. By cooperating with c-Myc, Kaposin B triggers angiogenesis by mediating the expression of cellular miRNAs in endothelial cells [296].

In the latent phase, KSHV also expresses vIRF3 (LANA-2) in PEL cells [71]. vIRF3 plays a major role in PEL pathogenesis by promoting viral latency and inhibiting the host innate responses. By stabilizing HIF-1α, vIRF3 induces its accumulation and activation in the nucleus contributing to the uncontrolled expression of VEGF in KSHV-infected cells [297].

2.6.3. Viral Lytic Genes Involved in Inflammation

ORF-K15, predominantly expressed during the lytic cycle, mediates inflammation by activating MAPK, JNK, and NF-κB pathways as well as NFAT/AP1 activities [298, 299]. These signaling pathways induce the expression of cytokines and chemokines such as IL-6, IL-1β, IL-8, CCL20, CXCL3, and COX-2. Depletion of ORF-K15 dramatically impairs KSHV-induced angiogenesis mediated by the recruitment of PLCγ1 and the activation of NFAT1-dependant RCAN1 expression in endothelial cells [300].

As stated earlier, ORF-K1 participates in KSHV-induced tumorigenesis by performing multiple functions. Among them, ORF-K1 induces the secretion of VEGF, IL-6, GM-CSF,

IL-1β, IL-8, and IL-10 in endothelial cells [301], and stimulates the expression of MMP-9, a matrix metalloproteinase involved in the angiogenic switch during tumor progression [302, 303]. In AIDS-related KS, ORF-K1 can synergize with HIV-1 proteins such as Tat to promote inflammation by activating NF-κB signaling [304] and NEF to promote cellular proliferation, vascular tube formation, and angiogenesis by regulating the PTEN/AKT/mTOR pathway [305]. In addition to inhibition of innate and adaptive immune responses, ORF-K5 enhances angiogenesis by disrupting VE-cadherin/β-catenin signaling, promoting the remodeling of cellular tight junctions [306]. vIL6 promotes angiogenesis and hematopoiesis by stimulating the secretion of VEGF [307]. By inducing several signaling pathways such as PKC, MAPK, mTOR, NF-κB, AP1, HIF-1α, and NFAT, vGPCR mediates the upregulation of pro-inflammatory and pro-angiogenic mediators (IL-2, IL-4, IL-6, IL-8, TNF-α, and VEGF) [308, 309]. vGPCR activation of NF-κB induces the expression of RANTES, IL-8, and GM-CSF as well as adhesion molecules VCAM-1, ICAM-1 and E-selectin [310].

KSHV encodes three homologues of cellular chemokines: vCCL1, vCCL2, and vCCL3. These viral chemokines activate their respective G-coupled protein receptors CCR8, CCR3 and CCR4 expressed on Th2 lymphocytes [311]. These viral chemokines inhibit T cells immune response by inducing Th2 polarization and attracting Th2 lymphocytes to the site of infection, and promoting angiogenesis by inducing the expression of VEGF [312, 313]. Moreover, vCCL2 antagonize CCR1 and CCR5 to inhibit host immune responses of Th1 lymphocytes [314].

2.7. KSHV and Metabolism

During latent infection and cellular transformation, KSHV reprograms cellular metabolic pathways to provide biosynthetic and bioenergetic precursors to support the fast anabolic cellular proliferation. During viral lytic replication, KSHV also reprograms specific metabolic pathways to support the production of infectious virions.

2.7.1. KSHV Reprograms Glucose Metabolism

A hallmark of tumorigenesis involves the switch of energy metabolism from oxidative phosphorylation to aerobic glycolysis. In untransformed telomerase-immortalized microvascular endothelial cells (TIME cells) and primary dermal microvascular endothelial cells (DMVECs), KSHV infection increases aerobic glycolysis by upregulating hexokinase 2 (HK2) and glucose transporter 3 (GLUT3) [315]. Thus, oxygen consumption and oxidative phosphorylation are decreased, and lactate production is increased. Inhibition of glycolysis leads to apoptosis in KSHV-infected TIME cells but not in uninfected cells, demonstrating the critical role of the aerobic glycolysis on cell survival in untransformed KSHV-infected cells [315]. A similar study in KSHV-infected primary dermal microvascular lymphatic endothelial cells (KLEC) also demonstrated increased aerobic glycolysis [316]. Mechanistically, KSHV miRNAs stabilize HIF-1α and inhibit mitochondrial biogenesis by downregulating EGLN2 and HSPA9. Moreover, HIF-1α is stabilized in KSHV-infected telomerase-immortalized HUVEC (TIVE) cells, which results in the upregulation of

glycolytic effector-isoform 2 of pyruvate kinase (PKM2) and increased aerobic glycolysis [316].

However, KSHV-induced glycolysis does not occur in HFF cells [315], which implies cell type specificity in KSHV-induced metabolic reprogramming. In contrast to untransformed KSHV-infected cells, KSHV-transformed KMM cells have reduced glucose and oxygen consumption, lactate production, and intracellular ATP [240]. Mechanistically, vFLIP and the miRNA cluster inhibit the aerobic glycolysis in KMM cells by downregulating glucose transporters GLUT1 and GLUT3 through NF-κB activation. The decreased glycolytic flux confers a survival advantage to KMM cells in a nutrient deficient tumor microenvironment [240].

2.7.2. KSHV Reprogramming of Glutamine Metabolism for Host Cell Proliferation and Survival

Glutamine is required for cancer cell proliferation and survival [317, 318]. KSHV infection increases both the intracellular glutamine levels and glutamine uptake in TIME cells. KSHV-infected TIME cells rely on glutamine for their survival and glutamine deprivation-induced apoptosis in KSHV-infected TIME cells with a lesser effect on TIME cells [319]. Suppressing glutaminolytic enzymes in the presence of glutamine causes cell death at the similar levels to those deprived of glutamine in KSHV-infected TIME cells with little effect on TIME cells. The sensitivity to the absence of glutamine can be restored by the addition of TCA cycle intermediates, indicating that in untransformed cells, glutaminolysis is required for cell survivals by feeding the TCA cycle through anaplerosis [319].

KSHV-transformed KMM cells also rely on glutamine for their proliferation and transformation. The expression of glutaminolytic enzymes is upregulated in KMM cells compared to MM cells, and inhibition of any of those enzymes reduces KMM cell proliferation, implying glutaminolysis is required for KMM cell survival [320]. Interestingly, the addition of carbon sources, such as TCA intermediates, only partially rescues the proliferation of KMM cells following glutamine depletion. In contrast, nonessential amino acid asparagine fully rescues the effects of glutamine deprivation, indicating that glutamine and asparagine provide not only carbon source but also nitrogen source [320]. Specifically, glutamine provides the γ-nitrogen for nucleotide synthesis in KSHV-transformed cells. Overall, KSHV reprograms glutaminolysis to supply the building blocks for synthesizing nucleotides, nonessential amino acids, and TCA cycle intermediates to support KSHV-infected cell proliferation and transformation [320].

2.7.3. KSHV Infection Induces Lipogenesis

KSHV infection of TIME cells induces lipogenesis with an increase of metabolites involved in de novo fatty acid synthesis (FAS) and formation of lipid droplets [321]. Inhibitors of FAS induce a dose-dependent cell death in KSHV-infected TIME, which can be partially rescued by supplying cells with fatty acid precursors, indicating FAS is necessary for the survival of untransformed KSHV-infected TIME cells [321]. A separate study shows that KSHV infection increases peroxisomes in TIME cells [322]. A major function of peroxisomes is to break down the long-chain fatty acids through β-oxidation. Inhibition of enzymes involved

in the peroxisomal β-oxidation leads to increased cell death in KSHV-infected TIME cells. Together, these observations suggest that KSHV-induced FAS and peroxisomal lipid metabolism are required for KSHV-infected TIME cell survival [322]. Additionally, PEL cells also have highly upregulated FAS compared to primary B cells and are sensitive to FAS inhibitors [323].

2.7.4. KSHV Depends on Glycolysis, Glutaminolysis, and FAS for Lytic Replication

Reprogramming of metabolic pathways is expected to be important for supporting KSHV lytic replication. However, there is so far limited work on metabolic rewiring during KSHV primary infection and reactivation. Inhibitors of glycolysis, glutaminolysis, and FAS significantly reduce the production of virions in both endothelial and SLK cells [324]. Inhibition of glycolysis and glutaminolysis suppresses KSHV replication by stalling early gene transcription and translation, respectively [324]. While inhibition of FAS decreases the production of extracellular virions, it does not affect intracellular viral genome levels, suggesting that FAS is required for virion assembly and maturation [324]. However, some of these inhibitors are not entirely specific and the mechanisms underlying the support of viral lytic replication by glycolysis and glutaminolysis remain unclear. Nevertheless, these results indicate that different stages of viral lytic replication might require different metabolites within the host cells.

2.8. Conclusion and Perspectives

Rapid progresses have been made in the KSHV field in the last decade, providing insights into the biology of virus and the scientific basis for developing novel therapeutic approaches for its associated malignancies. KSHV has evolved to hijack cellular machinery for completing its life cycle, which often results in the dysregulation of cellular functions. It is now clear that KSHV-induced uncontrolled cellular proliferation, cell survival, abnormal immune responses, and reprogrammed metabolism promote malignant tumor growth, angiogenesis, and inflammation, which are the hallmarks of KS.

The standard KS chemotherapy with liposomal doxorubicin, daunorubicin, or taxol is highly toxic and ineffective despite effective antiretroviral therapy in some cases [325]. Both PEL and MCD also do not any have effective therapy [326]. Therefore, alternative treatments and new therapeutic targets, particularly those targeting malignant proliferation, angiogenesis, inflammation, and dysregulated immune responses, are needed for KSHV-associated malignancies. Laboratory studies have so far identified numerous new targets and agents. These include sirtuin inhibitors (Tenovin-6 and nicotinamide), HDACs inhibitor, AMPK inhibitor, mTOR inhibitor Rapamycin (sirolimus), and p53 activator Nutlin-3 [264, 265, 266, 327, 328, 329, 330, 331]. Numerous potential therapeutic targets, particularly those targeting KSHV-specific epigenetics and metabolism, are attractive. Nevertheless, rigorous clinical trials are required to evaluate the efficacies of the inhibitors before their extensive usages in the patients. In fact, new drugs bevacizumab and imatinib for KS, and siltuximab for KSHV-MCD have been examined in clinical trials [332, 333, 334]. Ongoing clinical trials are testing the efficacies of Tocilizumab (NCT01441063) for MCD, and lenalidomide (NCT01057121) and pomalidomide (NCT02659930) for KS [335]. Because cellular

pathways often interact with one another, it would be interesting to evaluate interaction effects of multiple pathways and inhibitors. For example, while Rapamycin inhibits the mTOR pathway, it also activates the Akt pathway. Hence, the combination of inhibitors of both pathways would be predicted to be favorable, which has been demonstrated for both KS and PEL cells [267, 336].

Since KSHV is not a ubiquitous herpesvirus and immunosuppression is required for the development of the KSHV-associated malignancies, it would be essential to develop effective strategies to prevent its person-to-person transmission and manage immunosuppression in the affected populations. Development of KSHV vaccines should be one of the focuses of future research.

References

1. Chang Y, Cesarman E, Pessin MS, Lee F, Culpepper J, Knowles DM, Moore PS (1994) Identification of herpesvirus-like DNA sequences in AIDS-associated Kaposi's sarcoma. Science 266:1865–1869 [PubMed: 7997879]
2. Cesarman E, Chang Y, Moore PS, Said JW, Knowles DM (1995) Kaposi's sarcoma-associated herpesvirus-like DNA sequences in AIDS-related body-cavity-based lymphomas. N Engl J Med 332:1186–1191 [PubMed: 7700311]
3. Soulier J, Grollet L, Oksenhendler E, Cacoub P, Cazals-Hatem D, Babinet P, d'Agay MF, Clauvel JP, Raphael M, Degos L et al. (1995) Kaposi's sarcoma-associated herpesvirus-like DNA sequences in multicentric Castleman's disease. Blood 86:1276–1280 [PubMed: 7632932]
4. Uldrick TS, Wang V, O'Mahony D, Aleman K, Wyvill KM, Marshall V, Steinberg SM, Pittaluga S, Maric I, Whitby D, Tosato G, Little RF, Yarchoan R (2010) 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 51:350–358 [PubMed: 20583924]
5. Greene W, Kuhne K, Ye F, Chen J, Zhou F, Lei X, Gao SJ (2007) Molecular biology of KSHV in relation to AIDS-associated oncogenesis. Cancer Treat Res 133:69–127 [PubMed: 17672038]
6. Robey RC, Bower M (2015) Facing up to the ongoing challenge of Kaposi's sarcoma. Curr Opin Infect Dis 28:31–40 [PubMed: 25490104]
7. Okada S, Goto H, Yotsumoto M (2014) Current status of treatment for primary effusion lymphoma. Intractable Rare Dis Res 3:65–74 [PubMed: 25364646]
8. Carbone A, De Paoli P, Gloghini A, Vaccher E (2015) KSHV-associated multicentric Castleman disease: a tangle of different entities requiring multitarget treatment strategies. Int J Cancer 137:251–261 [PubMed: 24771491]
9. Polizzotto MN, Uldrick TS, Hu D, Yarchoan R (2012) Clinical Manifestations of Kaposi Sarcoma Herpesvirus Lytic Activation: Multicentric Castleman Disease (KSHV-MCD) and the KSHV Inflammatory Cytokine Syndrome. Front Microbiol 3:73 [PubMed: 22403576]
10. Tso FY, Sawyer A, Kwon EH, Mudenda V, Langford D, Zhou Y, West J, Wood C (2016) Kaposi's sarcoma-associated herpesvirus infection of neurons in HIV positive patients. J Infect Dis
11. Bechtel JT, Liang Y, Hvidding J, Ganem D (2003) Host range of Kaposi's sarcoma-associated herpesvirus in cultured cells. J Virol 77:6474–6481 [PubMed: 12743304]
12. Hahn AS, Kaufmann JK, Wies E, Naschberger E, Panteleev-Ivlev J, Schmidt K, Holzer A, Schmidt M, Chen J, Konig S, Ensser A, Myoung J, Brockmeyer NH, Sturzl M, Fleckenstein B, Neipel F (2012) The ephrin receptor tyrosine kinase A2 is a cellular receptor for Kaposi's sarcoma-associated herpesvirus. Nat Med 18:961–966 [PubMed: 22635007]
13. Akula SM, Pramod NP, Wang FZ, Chandran B (2002) Integrin alpha3beta1 (CD 49c/29) is a cellular receptor for Kaposi's sarcoma-associated herpesvirus (KSHV/HHV-8) entry into the target cells. Cell 108:407–419 [PubMed: 11853674]

14. Jones T, Ye F, Bedolla R, Huang Y, Meng J, Qian L, Pan H, Zhou F, Moody R, Wagner B, Arar M, Gao SJ (2012) Direct and efficient cellular transformation of primary rat mesenchymal precursor cells by KSHV. J Clin Invest 122:1076–1081 [PubMed: 22293176]
15. Foglieni C, Scabini S, Belloni D, Broccolo F, Lusso P, Malnati MS, Ferrero E (2005) Productive infection of HUVEC by HHV-8 is associated with changes compatible with angiogenic transformations. Eur J Histochem 49:273–284 [PubMed: 16216813]
16. Gao SJ, Deng JH, Zhou FC (2003) Productive lytic replication of a recombinant Kaposi's sarcoma-associated herpesvirus in efficient primary infection of primary human endothelial cells. J Virol 77:9738–9749 [PubMed: 12941882]
17. Kumar B, Chandran B (2016) KSHV entry and trafficking in target cells-hijacking of cell signal pathways, actin and membrane dynamics. Viruses 8
18. Zhang W, Gao SJ (2012) Exploitation of cellular cytoskeletons and signaling pathways for cell entry by Kaposi's sarcoma-associated herpesvirus and the closely related rhesus rhadinovirus. Pathogens 1:102–127 [PubMed: 23420076]
19. Akula SM, Wang FZ, Vieira J, Chandran B (2001) Human herpesvirus 8 interaction with target cells involves heparan sulfate. Virology 282:245–255 [PubMed: 11289807]
20. Hahn A, Birkmann A, Wies E, Dorer D, Mahr K, Sturzl M, Titgemeyer F, Neipel F (2009) Kaposi's sarcoma-associated herpesvirus gH/gL: glycoprotein export and interaction with cellular receptors. J Virol 83:396–407 [PubMed: 18945775]
21. Wang FZ, Akula SM, Pramod NP, Zeng L, Chandran B (2001) Human herpesvirus 8 envelope glycoprotein K8.1A interaction with the target cells involves heparan sulfate. J Virol 75:7517–7527 [PubMed: 11462024]
22. Birkmann A, Mahr K, Ensser A, Yaguboglu S, Titgemeyer F, Fleckenstein B, Neipel F (2001) Cell surface heparan sulfate is a receptor for human herpesvirus 8 and interacts with envelope glycoprotein K8.1. J Virol 75:11583–11593 [PubMed: 11689640]
23. Kerur N, Veettil MV, Sharma-Walia N, Sadagopan S, Bottero V, Paul AG, Chandran B (2010) Characterization of entry and infection of monocytic THP-1 cells by Kaposi's sarcoma associated herpesvirus (KSHV): role of heparan sulfate, DC-SIGN, integrins and signaling. Virology 406:103–116 [PubMed: 20674951]
24. Veettil MV, Sadagopan S, Sharma-Walia N, Wang FZ, Raghu H, Varga L, Chandran B (2008) Kaposi's sarcoma-associated herpesvirus forms a multimolecular complex of integrins (alphaVbeta5, alphaVbeta3, and alpha3beta1) and CD98-xCT during infection of human dermal microvascular endothelial cells, and CD98-xCT is essential for the postentry stage of infection. J Virol 82:12126–12144 [PubMed: 18829766]
25. Garrigues HJ, DeMaster LK, Rubinchikova YE, Rose TM (2014) KSHV attachment and entry are dependent on alphaVbeta3 integrin localized to specific cell surface microdomains and do not correlate with the presence of heparan sulfate. Virology 464–465:118–133
26. Rappocciolo G, Hensler HR, Jais M, Reinhart TA, Pegu A, Jenkins FJ, Rinaldo CR (2008) Human herpesvirus 8 infects and replicates in primary cultures of activated B lymphocytes through DC-SIGN. J Virol 82:4793–4806 [PubMed: 18337571]
27. Rappocciolo G, Jenkins FJ, Hensler HR, Piazza P, Jais M, Borowski L, Watkins SC, Rinaldo CR Jr (2006) DC-SIGN is a receptor for human herpesvirus 8 on dendritic cells and macrophages. J Immunol 176:1741–1749 [PubMed: 16424204]
28. Lewerenz J, Hewett SJ, Huang Y, Lambros M, Gout PW, Kalivas PW, Massie A, Smolders I, Methner A, Pergande M, Smith SB, Ganapathy V, Maher P (2013) The cystine/glutamate antiporter system x(c)(-) in health and disease: from molecular mechanisms to novel therapeutic opportunities. Antioxid Redox Signal 18:522–555 [PubMed: 22667998]
29. Kaleeba JA, Berger EA (2006) Kaposi's sarcoma-associated herpesvirus fusion-entry receptor: cystine transporter xCT. Science 311:1921–1924 [PubMed: 16574866]
30. Hahn AS, Desrosiers RC (2014) Binding of the Kaposi's sarcoma-associated herpesvirus to the ephrin binding surface of the EphA2 receptor and its inhibition by a small molecule. J Virol 88:8724–8734 [PubMed: 24899181]

31. Chakraborty S, Veettil MV, Bottero V, Chandran B (2012) Kaposi's sarcoma-associated herpesvirus interacts with EphrinA2 receptor to amplify signaling essential for productive infection. Proc Natl Acad Sci U S A 109:E1163–72 [PubMed: 22509030]
32. Dutta D, Chakraborty S, Bandyopadhyay C, Valiya Veettil M, Ansari MA, Singh VV, Chandran B (2013) EphrinA2 regulates clathrin mediated KSHV endocytosis in fibroblast cells by coordinating integrin-associated signaling and c-Cbl directed polyubiquitination. PLoS Pathog 9:e1003510 [PubMed: 23874206]
33. Akula SM, Naranatt PP, Walia NS, Wang FZ, Fegley B, Chandran B (2003) Kaposi's sarcoma-associated herpesvirus (human herpesvirus 8) infection of human fibroblast cells occurs through endocytosis. J Virol 77:7978–7990 [PubMed: 12829837]
34. Greene W, Gao SJ (2009) Actin dynamics regulate multiple endosomal steps during Kaposi's sarcoma-associated herpesvirus entry and trafficking in endothelial cells. PLoS Pathog 5:e1000512 [PubMed: 19593382]
35. Inoue N, Winter J, Lal RB, Offermann MK, Koyano S (2003) Characterization of entry mechanisms of human herpesvirus 8 by using an Rta-dependent reporter cell line. J Virol 77:8147–8152 [PubMed: 12829853]
36. Raghu H, Sharma-Walia N, Veettil MV, Sadagopan S, Chandran B (2009) 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 83:4895–4911 [PubMed: 19279100]
37. Valiya Veettil M, Sadagopan S, Kerur N, Chakraborty S, Chandran B (2010) Interaction of c-Cbl with myosin IIA regulates Bleb associated macropinocytosis of Kaposi's sarcoma-associated herpesvirus. PLoS Pathog 6:e1001238 [PubMed: 21203488]
38. Veettil MV, Kumar B, Ansari MA, Dutta D, Iqbal J, Gjyshi O, Bottero V, Chandran B (2016) ESCRT-0 component Hrs Promotes Macropinocytosis of Kaposi's Sarcoma-associated herpesvirus in human dermal microvascular endothelial cells. J Virol 90:3860–3872 [PubMed: 26819309]
39. Kumar B, Dutta D, Iqbal J, Ansari MA, Roy A, Chikoti L, Pisano G, Veettil MV, Chandran B (2016) ESCRT-I protein Tsg101 plays a role in the post-macropinocytic trafficking and infection of endothelial cells by Kaposi's sarcoma-associated herpesvirus. PLoS Pathog 12:e1005960 [PubMed: 27764233]
40. Naranatt PP, Krishnan HH, Smith MS, Chandran B (2005) 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 79:1191–1206 [PubMed: 15613346]
41. Sharma-Walia N, Naranatt PP, Krishnan HH, Zeng L, Chandran B (2004) 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 78:4207–4223 [PubMed: 15047836]
42. Krishnan HH, Sharma-Walia N, Streblow DN, Naranatt PP, Chandran B (2006) Focal adhesion kinase is critical for entry of Kaposi's sarcoma-associated herpesvirus into target cells. J Virol 80:1167–1180 [PubMed: 16414994]
43. Naik MU, Naik UP (2003) Calcium-and integrin-binding protein regulates focal adhesion kinase activity during platelet spreading on immobilized fibrinogen. Blood 102:3629–3636 [PubMed: 12881299]
44. Naik MU, Naik UP (2011) Contra-regulation of calcium- and integrin-binding protein 1-induced cell migration on fibronectin by PAK1 and MAP kinase signaling. J Cell Biochem 112:3289–3299 [PubMed: 21748785]
45. Bandyopadhyay C, Valiya-Veettil M, Dutta D, Chakraborty S, Chandran B (2014) CIB1 synergizes with EphrinA2 to regulate Kaposi's sarcoma-associated herpesvirus macropinocytic entry in human microvascular dermal endothelial cells. PLoS Pathog 10:e1003941 [PubMed: 24550731]
46. Chakraborty S, ValiyaVeettil M, Sadagopan S, Paudel N, Chandran B (2011) c-Cbl-mediated selective virus-receptor translocations into lipid rafts regulate productive Kaposi's sarcoma-associated herpesvirus infection in endothelial cells. J Virol 85:12410–12430 [PubMed: 21937638]

47. Greene W, Zhang W, He M, Witt C, Ye F, Gao SJ (2012) The ubiquitin/proteasome system mediates entry and endosomal trafficking of Kaposi's sarcoma-associated herpesvirus in endothelial cells. PLoS Pathog 8:e1002703 [PubMed: 22615563]
48. Bottero V, Chakraborty S, Chandran B (2013) Reactive oxygen species are induced by Kaposi's sarcoma-associated herpesvirus early during primary infection of endothelial cells to promote virus entry. J Virol 87:1733–1749 [PubMed: 23175375]
49. Pan H, Xie J, Ye F, Gao SJ (2006) 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 80:5371–5382 [PubMed: 16699017]
50. Sharma-Walia N, Krishnan HH, Naranatt PP, Zeng L, Smith MS, Chandran B (2005) 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 79:10308–10329 [PubMed: 16051824]
51. Xie J, Pan H, Yoo S, Gao SJ (2005) 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 79:15027–15037 [PubMed: 16306573]
52. Qin Z, Dai L, Defee M, Findlay VJ, Watson DK, Toole BP, Cameron J, Peruzzi F, Kirkwood K, Parsons C (2013) Kaposi's sarcoma-associated herpesvirus suppression of DUSP1 facilitates cellular pathogenesis following de novo infection. J Virol 87:621–635 [PubMed: 23097457]
53. Cheng F, Sawant TV, Lan K, Lu C, Jung JU, Gao SJ (2015) Screening of the human kinome identifies MSK1/2-CREB1 as an essential pathway mediating Kaposi's sarcoma-associated herpesvirus lytic replication during primary infection. J Virol 89:9262–9280 [PubMed: 26109721]
54. Cheng F, He M, Jung JU, Lu C, Gao SJ (2016) Suppression of Kaposi's sarcoma-associated herpesvirus infection and replication by 5'-AMP-activated protein kinase. J Virol 90:6515–6525 [PubMed: 27147746]
55. Sadagopan S, Sharma-Walia N, Veettil MV, Raghu H, Sivakumar R, Bottero V, Chandran B (2007) 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 81:3949–3968 [PubMed: 17287275]
56. Gjyshi O, Bottero V, Veettil MV, Dutta S, Singh VV, Chikoti L, Chandran B (2014) Kaposi's sarcoma-associated herpesvirus induces Nrf2 during de novo infection of endothelial cells to create a microenvironment conducive to infection. PLoS Pathog 10:e1004460 [PubMed: 25340789]
57. Yoo SM, Zhou FC, Ye FC, Pan HY, Gao SJ (2005) 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 343:47–64 [PubMed: 16154170]
58. Krishnan HH, Naranatt PP, Smith MS, Zeng L, Bloomer C, Chandran B (2004) 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 78:3601–3620 [PubMed: 15016882]
59. Purushothaman P, Thakker S, Verma SC (2015) Transcriptome analysis of Kaposi's sarcoma-associated herpesvirus during de novo primary infection of human B and endothelial cells. J Virol 89:3093–3111 [PubMed: 25552714]
60. Toth Z, Brulois K, Lee HR, Izumiya Y, Tepper C, Kung HJ, Jung JU (2013) Biphasic euchromatin-to-heterochromatin transition on the KSHV genome following de novo infection. PLoS Pathog 9:e1003813 [PubMed: 24367262]
61. Gunther T, Grundhoff A (2010) The epigenetic landscape of latent Kaposi's sarcoma-associated herpesvirus genomes. PLoS Pathog 6:e1000935 [PubMed: 20532208]
62. Toth Z, Maglinte DT, Lee SH, Lee HR, Wong LY, Brulois KF, Lee S, Buckley JD, Laird PW, Marquez VE, Jung JU (2010) Epigenetic analysis of KSHV latent and lytic genomes. PLoS Pathog 6:e1001013 [PubMed: 20661424]

63. Toth Z, Papp B, Brulois K, Choi YJ, Gao SJ, Jung JU (2016) LANA-mediated recruitment of host polycomb repressive complexes onto the KSHV genome during de novo infection. PLoS Pathog 12:e1005878 [PubMed: 27606464]
64. Singh VV, Dutta D, Ansari MA, Dutta S, Chandran B (2014) Kaposi's sarcoma-associated herpesvirus induces the ATM and H2AX DNA damage response early during de novo infection of primary endothelial cells, which play roles in latency establishment. J Virol 88:2821–2834 [PubMed: 24352470]
65. Ye F, Lei X, Gao SJ (2011) Mechanisms of Kaposi's sarcoma-associated herpesvirus latency and reactivation. Adv Virol
66. Dittmer D, Lagunoff M, Renne R, Staskus K, Haase A, Ganem D (1998) A cluster of latently expressed genes in Kaposi's sarcoma-associated herpesvirus. J Virol 72:8309–8315 [PubMed: 9733875]
67. Pearce M, Matsumura S, Wilson AC (2005) Transcripts encoding K12, v-FLIP, v-cyclin, and the microRNA cluster of Kaposi's sarcoma-associated herpesvirus originate from a common promoter. J Virol 79:14457–14464 [PubMed: 16254382]
68. Sarid R, Wiezorek JS, Moore PS, Chang Y (1999) Characterization and cell cycle regulation of the major Kaposi's sarcoma-associated herpesvirus (human herpesvirus 8) latent genes and their promoter. J Virol 73:1438–1446 [PubMed: 9882349]
69. Staudt MR, Dittmer DP (2006) Promoter switching allows simultaneous transcription of LANA and K14/vGPCR of Kaposi's sarcoma-associated herpesvirus. Virology 350:192–205 [PubMed: 16616289]
70. Samols MA, Hu J, Skalsky RL, Renne R (2005) Cloning and identification of a microRNA cluster within the latency-associated region of Kaposi's sarcoma-associated herpesvirus. J Virol 79:9301–9305 [PubMed: 15994824]
71. Cunningham C, Barnard S, Blackbourn DJ, Davison AJ (2003) Transcription mapping of human herpesvirus 8 genes encoding viral interferon regulatory factors. J Gen Virol 84:1471–1483 [PubMed: 12771416]
72. Gao S-J, Kingsley L, Hoover DR, Spira TJ, Rinaldo CR, Saah A, Phair J, Detels R, Parry P, Chang Y, Moore PS (1996) Seroconversion to antibodies against Kaposi's sarcoma-associated herpesvirus-related latent nuclear antigens before the development of Kaposi's sarcoma. N Engl J Med 335:233–241 [PubMed: 8657239]
73. Gao SJ, Kingsley L, Li M, Zheng W, Parravicini C, Ziegler J, Newton R, Rinaldo CR, Saah A, Phair J, Detels R, Chang Y, Moore PS (1996) KSHV antibodies among Americans, Italians and Ugandans with and without Kaposi's sarcoma. Nat Med 2:925–928 [PubMed: 8705864]
74. Kedes DH, Operskalski E, Busch M, Kohn R, Flood J, Ganem D (1996) The seroepidemiology of human herpesvirus 8 (Kaposi's sarcoma-associated herpesvirus): distribution of infection in KS risk groups and evidence for sexual transmission. Nat Med 2:918–924 [PubMed: 8705863]
75. Zhang YJ, Deng JH, Rabkin C, Gao SJ (2000) Hot-spot variations of Kaposi's sarcoma-associated herpesvirus latent nuclear antigen and application in genotyping by PCR-RFLP. J Gen Virol 81:2049–2058 [PubMed: 10900044]
76. Kwun HJ, da Silva SR, Qin H, Ferris RL, Tan R, Chang Y, Moore PS (2011) The central repeat domain 1 of Kaposi's sarcoma-associated herpesvirus (KSHV) latency associated-nuclear antigen 1 (LANA1) prevents cis MHC class I peptide presentation. Virology 412:357–365 [PubMed: 21324504]
77. Kwun HJ, da Silva SR, Shah IM, Blake N, Moore PS, Chang Y (2007) Kaposi's sarcoma-associated herpesvirus latency-associated nuclear antigen 1 mimics Epstein-Barr virus EBNA1 immune evasion through central repeat domain effects on protein processing. J Virol 81:8225–8235 [PubMed: 17522213]
78. Canham M, Talbot SJ (2004) A naturally occurring C-terminal truncated isoform of the latent nuclear antigen of Kaposi's sarcoma-associated herpesvirus does not associate with viral episomal DNA. J Gen Virol 85:1363–1369 [PubMed: 15166417]
79. Kwun HJ, Toptan T, Ramos da Silva S, Atkins JF, Moore PS, Chang Y (2014) Human DNA tumor viruses generate alternative reading frame proteins through repeat sequence recoding. Proc Natl Acad Sci U S A 111:E4342–9 [PubMed: 25271323]

80. Ballestas ME, Chatis PA, Kaye KM (1999) Efficient persistence of extrachromosomal KSHV DNA mediated by latency-associated nuclear antigen. Science 284:641–644 [PubMed: 10213686]
81. Ueda K, Sakakibara S, Ohsaki E, Yada K (2006) Lack of a mechanism for faithful partition and maintenance of the KSHV genome. Virus Res 122:85–94 [PubMed: 16920214]
82. Gao SJ, Zhang YJ, Deng JH, Rabkin CS, Flore O, Jenson HB (1999) Molecular polymorphism of Kaposi's sarcoma-associated herpesvirus (Human herpesvirus 8) latent nuclear antigen: evidence for a large repertoire of viral genotypes and dual infection with different viral genotypes. J Infect Dis 180:1466–1476 [PubMed: 10515805]
83. Ye FC, Zhou FC, Yoo SM, Xie JP, Browning PJ, Gao SJ (2004) Disruption of Kaposi's sarcoma-associated herpesvirus latent nuclear antigen leads to abortive episome persistence. J Virol 78:11121–11129 [PubMed: 15452232]
84. Cherezova L, Burnside KL, Rose TM (2011) Conservation of complex nuclear localization signals utilizing classical and non-classical nuclear import pathways in LANA homologs of KSHV and RFHV. PLoS ONE 6:e18920 [PubMed: 21559489]
85. Ballestas ME, Kaye KM (2001) 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 75:3250–3258 [PubMed: 11238851]
86. Barbera AJ, Chodaparambil JV, Kelley-Clarke B, Luger K, Kaye KM (2006) Kaposi's sarcoma-associated herpesvirus LANA hitches a ride on the chromosome. Cell Cycle 5:1048–1052 [PubMed: 16721045]
87. Barbera AJ, Chodaparambil JV, Kelley-Clarke B, Joukov V, Walter JC, Luger K, Kaye KM (2006) The nucleosomal surface as a docking station for Kaposi's sarcoma herpesvirus LANA. Science 311:856–861 [PubMed: 16469929]
88. Kelley-Clarke B, De Leon-Vazquez E, Slain K, Barbera AJ, Kaye KM (2009) Role of Kaposi's sarcoma-associated herpesvirus C-terminal LANA chromosome binding in episome persistence. J Virol 83:4326–4337 [PubMed: 19225000]
89. Lim C, Lee D, Seo T, Choi C, Choe J (2003) Latency-associated nuclear antigen of Kaposi's sarcoma-associated herpesvirus functionally interacts with heterochromatin protein 1. J Biol Chem 278:7397–7405 [PubMed: 12486118]
90. Pan HY, Zhang YJ, Wang XP, Deng JH, Zhou FC, Gao SJ (2003) Identification of a novel cellular transcriptional repressor interacting with the latent nuclear antigen of Kaposi's sarcoma-associated herpesvirus. J Virol 77:9758–9768 [PubMed: 12941884]
91. Matsumura S, Persson LM, Wong L, Wilson AC (2010) The latency-associated nuclear antigen interacts with MeCP2 and nucleosomes through separate domains. J Virol 84:2318–2330 [PubMed: 20032179]
92. Ottinger M, Christalla T, Nathan K, Brinkmann MM, Viejo-Borbolla A, Schulz TF (2006) Kaposi's sarcoma-associated herpesvirus LANA-1 interacts with the short variant of BRD4 and releases cells from a BRD4- and BRD2/RING3-induced G1 cell cycle arrest. J Virol 80:10772–10786 [PubMed: 16928766]
93. Xiao B, Verma SC, Cai Q, Kaul R, Lu J, Saha A, Robertson ES (2010) Bub1 and CENP-F can contribute to Kaposi's sarcoma-associated herpesvirus genome persistence by targeting LANA to kinetochores. J Virol 84:9718–9732 [PubMed: 20660191]
94. Si H, Verma SC, Lampson MA, Cai Q, Robertson ES (2008) Kaposi's sarcoma-associated herpesvirus-encoded LANA can interact with the nuclear mitotic apparatus protein to regulate genome maintenance and segregation. J Virol 82:6734–6746 [PubMed: 18417561]
95. Verma SC, Choudhuri T, Kaul R, Robertson ES (2006) Latency-associated nuclear antigen (LANA) of Kaposi's sarcoma-associated herpesvirus interacts with origin recognition complexes at the LANA binding sequence within the terminal repeats. J Virol 80:2243–2256 [PubMed: 16474132]
96. Lan K, Kuppers DA, Verma SC, Robertson ES (2004) Kaposi's sarcoma-associated herpesvirus-encoded latency-associated nuclear antigen inhibits lytic replication by targeting Rta: a potential mechanism for virus-mediated control of latency. J Virol 78:6585–6594 [PubMed: 15163750]
97. Li Q, Zhou F, Ye F, Gao SJ (2008) Genetic disruption of KSHV major latent nuclear antigen LANA enhances viral lytic transcriptional program. Virology 379:234–244 [PubMed: 18684478]

98. Li Q, He M, Zhou F, Ye F, Gao SJ (2014) Activation of Kaposi's sarcoma-associated herpesvirus (KSHV) by inhibitors of class III histone deacetylases: identification of sirtuin 1 as a regulator of the KSHV life cycle. J Virol 88:6355–6367 [PubMed: 24672028]

99. He M, Gao SJ (2014) A novel role of SIRT1 in gammaherpesvirus latency and replication. Cell Cycle 13:3328–3330 [PubMed: 25485577]

100. Stedman W, Deng Z, Lu F, Lieberman PM (2004) ORC, MCM, and histone hyperacetylation at the Kaposi's sarcoma-associated herpesvirus latent replication origin. J Virol 78:12566–12575 [PubMed: 15507644]

101. Lu F, Zhou J, Wiedmer A, Madden K, Yuan Y, Lieberman PM (2003) Chromatin remodeling of the Kaposi's sarcoma-associated herpesvirus ORF50 promoter correlates with reactivation from latency. J Virol 77:11425–11435 [PubMed: 14557628]

102. Chen J, Ueda K, Sakakibara S, Okuno T, Parravicini C, Corbellino M, Yamanishi K (2001) Activation of latent Kaposi's sarcoma-associated herpesvirus by demethylation of the promoter of the lytic transactivator. Proc Natl Acad Sci U S A 98:4119–4124 [PubMed: 11274437]

103. Ohsaki E, Ueda K, Sakakibara S, Do E, Yada K, Yamanishi K (2004) Poly(ADP-ribose) polymerase 1 binds to Kaposi's sarcoma-associated herpesvirus (KSHV) terminal repeat sequence and modulates KSHV replication in latency. J Virol 78:9936–9946 [PubMed: 15331727]

104. Hyun TS, Subramanian C, Cotter MA 2nd, Thomas RA, Robertson ES (2001) Latency-associated nuclear antigen encoded by Kaposi's sarcoma-associated herpesvirus interacts with Tat and activates the long terminal repeat of human immunodeficiency virus type 1 in human cells. J Virol 75:8761–8771 [PubMed: 11507221]

105. Garber AC, Shu MA, Hu J, Renne R (2001) DNA binding and modulation of gene expression by the latency-associated nuclear antigen of Kaposi's sarcoma-associated herpesvirus. J Virol 75:7882–7892 [PubMed: 11483733]

106. Stedman W, Kang H, Lin S, Kissil JL, Bartolomei MS, Lieberman PM (2008) Cohesins localize with CTCF at the KSHV latency control region and at cellular c-myc and H19/Igf2 insulators. EMBO J 27:654–666 [PubMed: 18219272]

107. Kang H, Lieberman PM (2009) Cell cycle control of Kaposi's sarcoma-associated herpesvirus latency transcription by CTCF-cohesin interactions. J Virol 83:6199–6210 [PubMed: 19369356]

108. Kang H, Wiedmer A, Yuan Y, Robertson E, Lieberman PM (2011) Coordination of KSHV latent and lytic gene control by CTCF-cohesin mediated chromosome conformation. PLoS Pathog 7:e1002140 [PubMed: 21876668]

109. Chen HS, Wikramasinghe P, Showe L, Lieberman PM (2012) Cohesins repress Kaposi's sarcoma-associated herpesvirus immediate early gene transcription during latency. J Virol 86:9454–9464 [PubMed: 22740398]

110. Kang H, Cho H, Sung GH, Lieberman PM (2013) CTCF regulates Kaposi's sarcoma-associated herpesvirus latency transcription by nucleosome displacement and RNA polymerase programming. J Virol 87:1789–1799 [PubMed: 23192870]

111. Ye FC, Zhou FC, Xie JP, Kang T, Greene W, Kuhne K, Lei XF, Li QH, Gao SJ (2008) Kaposi's sarcoma-associated herpesvirus latent gene vFLIP inhibits viral lytic replication through NF-kappaB-mediated suppression of the AP-1 pathway: a novel mechanism of virus control of latency. J Virol 82:4235–4249 [PubMed: 18305042]

112. Lei X, Bai Z, Ye F, Xie J, Kim CG, Huang Y, Gao SJ (2010) Regulation of NF-kappaB inhibitor IkappaBalpha and viral replication by a KSHV microRNA. Nat Cell Biol 12:193–199 [PubMed: 20081837]

113. Bellare P, Ganem D (2009) Regulation of KSHV lytic switch protein expression by a virus-encoded microRNA: an evolutionary adaptation that fine-tunes lytic reactivation. Cell Host Microbe 6:570–575 [PubMed: 20006845]

114. Lu CC, Li Z, Chu CY, Feng J, Sun R, Rana TM (2010) MicroRNAs encoded by Kaposi's sarcoma-associated herpesvirus regulate viral life cycle. EMBO Rep 11:784–790 [PubMed: 20847741]

115. Lu F, Stedman W, Yousef M, Renne R, Lieberman PM (2010) Epigenetic regulation of Kaposi's sarcoma-associated herpesvirus latency by virus-encoded microRNAs that target Rta and the cellular Rbl2-DNMT pathway. J Virol 84:2697–2706 [PubMed: 20071580]

116. Liang D, Gao Y, Lin X, He Z, Zhao Q, Deng Q, Lan K (2011) A human herpesvirus miRNA attenuates interferon signaling and contributes to maintenance of viral latency by targeting IKKepsilon. Cell Res 21:793–806 [PubMed: 21221132]

117. Lin X, Liang D, He Z, Deng Q, Robertson ES, Lan K (2011) miR-K12-7-5p encoded by Kaposi's sarcoma-associated herpesvirus stabilizes the latent state by targeting viral ORF50/RTA. PLoS ONE 6:e16224 [PubMed: 21283761]

118. Bai Z, Huang Y, Li W, Zhu Y, Jung JU, Lu C, Gao SJ (2014) Genomewide mapping and screening of Kaposi's sarcoma-associated herpesvirus (KSHV) 3′ untranslated regions identify bicistronic and polycistronic viral transcripts as frequent targets of KSHV microRNAs. J Virol 88:377–392 [PubMed: 24155407]

119. Arias C, Weisburd B, Stern-Ginossar N, Mercier A, Madrid AS, Bellare P, Holdorf M, Weissman JS, Ganem D (2014) KSHV 2.0: a comprehensive annotation of the Kaposi's sarcoma-associated herpesvirus genome using next-generation sequencing reveals novel genomic and functional features. PLoS Pathog 10:e1003847 [PubMed: 24453964]

120. Lukac DM, Renne R, Kirshner JR, Ganem D (1998) 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 252:304–312 [PubMed: 9878608]

121. Sun R, Lin SF, Gradoville L, Yuan Y, Zhu F, Miller G (1998) A viral gene that activates lytic cycle expression of Kaposi's sarcoma-associated herpesvirus. Proc Natl Acad Sci U S A 95:10866–10871 [PubMed: 9724796]

122. Gradoville L, Gerlach J, Grogan E, Shedd D, Nikiforow S, Metroka C, Miller G (2000) 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 74:6207–6212 [PubMed: 10846108]

123. Song MJ, Brown HJ, Wu TT, Sun R (2001) Transcription activation of polyadenylated nuclear rna by rta in human herpesvirus 8/Kaposi's sarcoma-associated herpesvirus. J Virol 75:3129–3140 [PubMed: 11238840]

124. Bu W, Palmeri D, Krishnan R, Marin R, Aris VM, Soteropoulos P, Lukac DM (2008) Identification of direct transcriptional targets of the Kaposi's sarcoma-associated herpesvirus Rta lytic switch protein by conditional nuclear localization. J Virol 82:10709–10723 [PubMed: 18715905]

125. Chen J, Ye F, Xie J, Kuhne K, Gao SJ (2009) Genome-wide identification of binding sites for Kaposi's sarcoma-associated herpesvirus lytic switch protein, RTA. Virology 386:290–302 [PubMed: 19233445]

126. Ziegelbauer J, Grundhoff A, Ganem D (2006) 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 80:2958–2967 [PubMed: 16501105]

127. Ye J, Shedd D, Miller G (2005) An Sp1 response element in the Kaposi's sarcoma-associated herpesvirus open reading frame 50 promoter mediates lytic cycle induction by butyrate. J Virol 79:1397–1408 [PubMed: 15650166]

128. Carroll KD, Khadim F, Spadavecchia S, Palmeri D, Lukac DM (2007) Direct interactions of Kaposi's sarcoma-associated herpesvirus/human herpesvirus 8 ORF50/Rta protein with the cellular protein octamer-1 and DNA are critical for specifying transactivation of a delayed-early promoter and stimulating viral reactivation. J Virol 81:8451–8467 [PubMed: 17537858]

129. Wilson SJ, Tsao EH, Webb BL, Ye H, Dalton-Griffin L, Tsantoulas C, Gale CV, Du MQ, Whitehouse A, Kellam P (2007) X box binding protein XBP-1 s transactivates the Kaposi's sarcoma-associated herpesvirus (KSHV) ORF50 promoter, linking plasma cell differentiation to KSHV reactivation from latency. J Virol 81:13578–13586 [PubMed: 17928342]

130. Chang PJ, Boonsiri J, Wang SS, Chen LY, Miller G (2010) Binding of RBP-Jkappa (CSL) protein to the promoter of the Kaposi's sarcoma-associated herpesvirus ORF47 (gL) gene is a critical but not sufficient determinant of transactivation by ORF50 protein. Virology 398:38–48 [PubMed: 20006367]

131. Wang SE, Wu FY, Fujimuro M, Zong J, Hayward SD, Hayward GS (2003) 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 77:600–623 [PubMed: 12477864]

132. Guito J, Lukac DM (2012) KSHV Rta promoter specification and viral reactivation. Front Microbiol 3:30 [PubMed: 22347875]

133. Sun Z, Jha HC, Pei YG, Robertson ES (2016) Major histocompatibility complex class II HLA-DRalpha is downregulated by Kaposi's Sarcoma-associated herpesvirus-encoded lytic transactivator RTA and MARCH8. J Virol 90:8047–8058 [PubMed: 27356905]

134. Chmura JC, Herold K, Ruffin A, Atuobi T, Fabiyi Y, Mitchell AE, Choi YB, Ehrlich ES (2017) The Itch ubiquitin ligase is required for KSHV RTA induced vFLIP degradation. Virology 501:119–126 [PubMed: 27912080]

135. Ehrlich ES, Chmura JC, Smith JC, Kalu NN, Hayward GS (2014) KSHV RTA abolishes NFkappaB responsive gene expression during lytic reactivation by targeting vFLIP for degradation via the proteasome. PLoS ONE 9:e91359 [PubMed: 24614587]

136. AuCoin DP, Colletti KS, Cei SA, Papouskova I, Tarrant M, Pari GS (2004) 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 318:542–555 [PubMed: 14972523]

137. Wang Y, Li H, Chan MY, Zhu FX, Lukac DM, Yuan Y (2004) Kaposi's sarcoma-associated herpesvirus ori-Lyt-dependent DNA replication: cis-acting requirements for replication and ori-Lyt-associated RNA transcription. J Virol 78:8615–8629 [PubMed: 15280471]

138. Wakeman BS, Izumiya Y, Speck SH (2016) Identification of novel KSHV Orf50 transcripts: discovery of new RTA isoforms with variable transactivation potential. J Virol

139. Han Z, Swaminathan S (2006) Kaposi's sarcoma-associated herpesvirus lytic gene ORF57 is essential for infectious virion production. J Virol 80:5251–5260 [PubMed: 16699005]

140. Majerciak V, Yamanegi K, Allemand E, Kruhlak M, Krainer AR, Zheng ZM (2008) Kaposi's sarcoma-associated herpesvirus ORF57 functions as a viral splicing factor and promotes expression of intron-containing viral lytic genes in spliceosome-mediated RNA splicing. J Virol 82:2792–2801 [PubMed: 18184716]

141. Malik P, Blackbourn DJ, Cheng MF, Hayward GS, Clements JB (2004) Functional co-operation between the Kaposi's sarcoma-associated herpesvirus ORF57 and ORF50 regulatory proteins. J Gen Virol 85:2155–2166 [PubMed: 15269354]

142. Majerciak V, Zheng ZM (2015) KSHV ORF57, a protein of many faces. Viruses 7:604–633 [PubMed: 25674768]

143. Pilkington GR, Majerciak V, Bear J, Uranishi H, Zheng ZM, Felber BK (2012) Kaposi's sarcoma-associated herpesvirus ORF57 is not a bona fide export factor. J Virol 86:13089–13094 [PubMed: 22993146]

144. Massimelli MJ, Kang JG, Majerciak V, Le SY, Liewehr DJ, Steinberg SM, Zheng ZM (2011) Stability of a long noncoding viral RNA depends on a 9-nt core element at the RNA 5′ end to interact with viral ORF57 and cellular PABPC1. Int J Biol Sci 7:1145–1160 [PubMed: 22043172]

145. Sei E, Conrad NK (2011) Delineation of a core RNA element required for Kaposi's sarcoma-associated herpesvirus ORF57 binding and activity. Virology 419:107–116 [PubMed: 21889182]

146. Kang JG, Pripuzova N, Majerciak V, Kruhlak M, Le SY, Zheng ZM (2011) Kaposi's sarcoma-associated herpesvirus ORF57 promotes escape of viral and human interleukin-6 from microRNA-mediated suppression. J Virol 85:2620–2630 [PubMed: 21209110]

147. Boyne JR, Jackson BR, Taylor A, Macnab SA, Whitehouse A (2010) Kaposi's sarcoma-associated herpesvirus ORF57 protein interacts with PYM to enhance translation of viral intronless mRNAs. EMBO J 29:1851–1864 [PubMed: 20436455]

148. Lin SF, Robinson DR, Miller G, Kung HJ (1999) Kaposi's sarcoma-associated herpesvirus encodes a bZIP protein with homology to BZLF1 of Epstein-Barr virus. J Virol 73:1909–1917 [PubMed: 9971770]

149. Purushothaman P, Uppal T, Verma SC (2015) Molecular biology of KSHV lytic reactivation. Viruses 7:116–153 [PubMed: 25594835]

150. Martinez FP, Tang Q (2012) Leucine zipper domain is required for Kaposi sarcoma-associated herpesvirus (KSHV) K-bZIP protein to interact with histone deacetylase and is important for KSHV replication. J Biol Chem 287:15622–15634 [PubMed: 22416134]

151. Izumiya Y, Ellison TJ, Yeh ET, Jung JU, Luciw PA, Kung HJ (2005) Kaposi's sarcoma-associated herpesvirus K-bZIP represses gene transcription via SUMO modification. J Virol 79:9912–9925 [PubMed: 16014952]

152. Chang PC, Izumiya Y, Wu CY, Fitzgerald LD, Campbell M, Ellison TJ, Lam KS, Luciw PA, Kung HJ (2010) Kaposi's sarcoma-associated herpesvirus (KSHV) encodes a SUMO E3 ligase that is SIM-dependent and SUMO-2/3-specific. J Biol Chem 285:5266–5273 [PubMed: 20034935]

153. Yang WS, Hsu HW, Campbell M, Cheng CY, Chang PC (2015) K-bZIP mediated SUMO-2/3 specific modification on the KSHV genome negatively regulates lytic gene expression and viral reactivation. PLoS Pathog 11:e1005051 [PubMed: 26197391]

154. Yang WS, Campbell M, Chang PC (2017) SUMO modification of a heterochromatin histone demethylase JMJD2A enables viral gene transactivation and viral replication. PLoS Pathog 13:e1006216 [PubMed: 28212444]

155. Rossetto C, Yamboliev I, Pari GS (2009) Kaposi's sarcoma-associated herpesvirus/human herpesvirus 8 K-bZIP modulates latency-associated nuclear protein-mediated suppression of lytic origin-dependent DNA synthesis. J Virol 83:8492–8501 [PubMed: 19553319]

156. Izumiya Y, Izumiya C, Van Geelen A, Wang DH, Lam KS, Luciw PA, Kung HJ (2007) Kaposi's sarcoma-associated herpesvirus-encoded protein kinase and its interaction with K-bZIP. J Virol 81:1072–1082 [PubMed: 17108053]

157. Toth Z, Brulois K, Jung JU (2013) The chromatin landscape of Kaposi's sarcoma-associated herpesvirus. Viruses 5:1346–1373 [PubMed: 23698402]

158. Gwack Y, Baek HJ, Nakamura H, Lee SH, Meisterernst M, Roeder RG, Jung JU (2003) Principal role of TRAP/mediator and SWI/SNF complexes in Kaposi's sarcoma-associated herpesvirus RTA-mediated lytic reactivation. Mol Cell Biol 23:2055–2067 [PubMed: 12612078]

159. Ye F, Zeng Y, Sha J, Jones T, Kuhne K, Wood C, Gao SJ (2016) High glucose induces reactivation of latent Kaposi's sarcoma-associated herpesvirus. J Virol 8 17. pii: JVI.01049–16. [Epub ahead of print]

160. Thakker S, Verma SC (2016) Co-infections and pathogenesis of KSHV-associated malignancies. Front Microbiol 7:151 [PubMed: 26913028]

161. Merat R, Amara A, Lebbe C, de The H, Morel P, Saib A (2002) HIV-1 infection of primary effusion lymphoma cell line triggers Kaposi's sarcoma-associated herpesvirus (KSHV) reactivation. Int J Cancer 97:791–795 [PubMed: 11857356]

162. Zeng Y, Zhang X, Huang Z, Cheng L, Yao S, Qin D, Chen X, Tang Q, Lv Z, Zhang L, Lu C (2007) Intracellular Tat of human immunodeficiency virus type 1 activates lytic cycle replication of Kaposi's sarcoma-associated herpesvirus: role of JAK/STAT signaling. J Virol 81:2401–2417 [PubMed: 17151125]

163. Aoki Y, Tosato G (2004) HIV-1 Tat enhances Kaposi sarcoma-associated herpesvirus (KSHV) infectivity. Blood 104:810–814 [PubMed: 15073028]

164. Spadavecchia S, Gonzalez-Lopez O, Carroll KD, Palmeri D, Lukac DM (2010) Convergence of Kaposi's sarcoma-associated herpesvirus reactivation with Epstein-Barr virus latency and cellular growth mediated by the notch signaling pathway in coinfected cells. J Virol 84:10488–10500 [PubMed: 20686042]

165. Jiang Y, Xu D, Zhao Y, Zhang L (2008) Mutual inhibition between Kaposi's sarcoma-associated herpesvirus and Epstein-Barr virus lytic replication initiators in dually-infected primary effusion lymphoma. PLoS ONE 3:e1569 [PubMed: 18253508]

166. Lu C, Zeng Y, Huang Z, Huang L, Qian C, Tang G, Qin D (2005) Human herpesvirus 6 activates lytic cycle replication of Kaposi's sarcoma-associated herpesvirus. Am J Pathol 166:173–183 [PubMed: 15632010]

167. Tang Q, Qin D, Lv Z, Zhu X, Ma X, Yan Q, Zeng Y, Guo Y, Feng N, Lu C (2012) Herpes simplex virus type 2 triggers reactivation of Kaposi's sarcoma-associated herpesvirus from latency and collaborates with HIV-1 Tat. PLoS ONE 7:e31652 [PubMed: 22347501]
168. Blauvelt A (2001) Skin diseases associated with human herpesvirus 6, 7, and 8 infection. J Investig Dermatol Symp Proc 6:197–202
169. Roupelieva M, Griffiths SJ, Kremmer E, Meisterernst M, Viejo-Borbolla A, Schulz T, Haas J (2010) Kaposi's sarcoma-associated herpesvirus Lana-1 is a major activator of the serum response element and mitogen-activated protein kinase pathways via interactions with the mediator complex. J Gen Virol 91:1138–1149 [PubMed: 20089804]
170. Vieira J, O'Hearn P, Kimball L, Chandran B, Corey L (2001) Activation of Kaposi's sarcoma-associated herpesvirus (human herpesvirus 8) lytic replication by human cytomegalovirus. J Virol 75:1378–1386 [PubMed: 11152511]
171. Wells R, Stensland L, Vieira J (2009) The human cytomegalovirus UL112-113 locus can activate the full Kaposi's sarcoma-associated herpesvirus lytic replication cycle. J Virol 83:4695–4699 [PubMed: 19211735]
172. Dai L, DeFee MR, Cao Y, Wen J, Wen X, Noverr MC, Qin Z (2014) Lipoteichoic acid (LTA) and lipopolysaccharides (LPS) from periodontal pathogenic bacteria facilitate oncogenic herpesvirus infection within primary oral cells. PLoS ONE 9:e101326 [PubMed: 24971655]
173. Morris TL, Arnold RR, Webster-Cyriaque J (2007) Signaling cascades triggered by bacterial metabolic end products during reactivation of Kaposi's sarcoma-associated herpesvirus. J Virol 81:6032–6042 [PubMed: 17376930]
174. Yu X, Shahir AM, Sha J, Feng Z, Eapen B, Nithianantham S, Das B, Karn J, Weinberg A, Bissada NF, Ye F (2014) Short-chain fatty acids from periodontal pathogens suppress histone deacetylases, EZH2, and SUV39H1 to promote Kaposi's sarcoma-associated herpesvirus replication. J Virol 88:4466–4479 [PubMed: 24501407]
175. Davis DA, Rinderknecht AS, Zoeteweij JP, Aoki Y, Read-Connole EL, Tosato G, Blauvelt A, Yarchoan R (2001) Hypoxia induces lytic replication of Kaposi sarcoma-associated herpesvirus. Blood 97:3244–3250 [PubMed: 11342455]
176. Haque M, Wang V, Davis DA, Zheng ZM, Yarchoan R (2006) Genetic organization and hypoxic activation of the Kaposi's sarcoma-associated herpesvirus ORF34-37 gene cluster. J Virol 80:7037–7051 [PubMed: 16809309]
177. Haque M, Davis DA, Wang V, Widmer I, Yarchoan R (2003) Kaposi's sarcoma-associated herpesvirus (human herpesvirus 8) contains hypoxia response elements: relevance to lytic induction by hypoxia. J Virol 77:6761–6768 [PubMed: 12767996]
178. Veeranna RP, Haque M, Davis DA, Yang M, Yarchoan R (2012) Kaposi's sarcoma-associated herpesvirus latency-associated nuclear antigen induction by hypoxia and hypoxia-inducible factors. J Virol 86:1097–1108 [PubMed: 22090111]
179. Cai Q, Lan K, Verma SC, Si H, Lin D, Robertson ES (2006) Kaposi's sarcoma-associated herpesvirus latent protein LANA interacts with HIF-1 alpha to upregulate RTA expression during hypoxia: Latency control under low oxygen conditions. J Virol 80:7965–7975 [PubMed: 16873253]
180. Dalton-Griffin L, Wilson SJ, Kellam P (2009) X-box binding protein 1 contributes to induction of the Kaposi's sarcoma-associated herpesvirus lytic cycle under hypoxic conditions. J Virol 83:7202–7209 [PubMed: 19403667]
181. Yu F, Feng J, Harada JN, Chanda SK, Kenney SC, Sun R (2007) B cell terminal differentiation factor XBP-1 induces reactivation of Kaposi's sarcoma-associated herpesvirus. FEBS Lett 581:3485–3488 [PubMed: 17617410]
182. Zhang L, Zhu C, Guo Y, Wei F, Lu J, Qin J, Banerjee S, Wang J, Shang H, Verma SC, Yuan Z, Robertson ES, Cai Q (2014) Inhibition of KAP1 enhances hypoxia-induced Kaposi's sarcoma-associated herpesvirus reactivation through RBP-Jkappa. J Virol 88:6873–6884 [PubMed: 24696491]
183. Sun R, Liang D, Gao Y, Lan K (2014) Kaposi's sarcoma-associated herpesvirus-encoded LANA interacts with host KAP1 to facilitate establishment of viral latency. J Virol 88:7331–7344 [PubMed: 24741090]

184. Ye F, Zhou F, Bedolla RG, Jones T, Lei X, Kang T, Guadalupe M, Gao SJ (2011) Reactive oxygen species hydrogen peroxide mediates Kaposi's sarcoma-associated herpesvirus reactivation from latency. PLoS Pathog 7:e1002054 [PubMed: 21625536]

185. Li X, Feng J, Sun R (2011) Oxidative stress induces reactivation of Kaposi's sarcoma-associated herpesvirus and death of primary effusion lymphoma cells. J Virol 85:715–724 [PubMed: 21068240]

186. Gao SJ, Boshoff C, Jayachandra S, Weiss RA, Chang Y, Moore PS (1997) KSHV ORF K9 (vIRF) is an oncogene which inhibits the interferon signaling pathway. Oncogene 15:1979–1985 [PubMed: 9365244]

187. Hwang SW, Kim D, Jung JU, Lee HR (2017) KSHV-encoded viral interferon regulatory factor 4 (vIRF4) interacts with IRF7 and inhibits interferon alpha production. Biochem Biophys Res Commun 486:700–705 [PubMed: 28342865]

188. Giffin L, Damania B (2014) KSHV: pathways to tumorigenesis and persistent infection. Adv Virus Res 88:111–159 [PubMed: 24373311]

189. Liang Q, Fu B, Wu F, Li X, Yuan Y, Zhu F (2012) ORF45 of Kaposi's sarcoma-associated herpesvirus inhibits phosphorylation of interferon regulatory factor 7 by IKKepsilon and TBK1 as an alternative substrate. J Virol 86:10162–10172 [PubMed: 22787218]

190. Yu Y, Wang SE, Hayward GS (2005) The KSHV immediate-early transcription factor RTA encodes ubiquitin E3 ligase activity that targets IRF7 for proteosome-mediated degradation. Immunity 22:59–70 [PubMed: 15664159]

191. Lefort S, Soucy-Faulkner A, Grandvaux N, Flamand L (2007) Binding of Kaposi's sarcoma-associated herpesvirus K-bZIP to interferon-responsive factor 3 elements modulates antiviral gene expression. J Virol 81:10950–10960 [PubMed: 17652396]

192. Bartee E, McCormack A, Fruh K (2006) Quantitative membrane proteomics reveals new cellular targets of viral immune modulators. PLoS Pathog 2:e107 [PubMed: 17238276]

193. Li Q, Means R, Lang S, Jung JU (2007) Downregulation of gamma interferon receptor 1 by Kaposi's sarcoma-associated herpesvirus K3 and K5. J Virol 81:2117–2127 [PubMed: 17166914]

194. Lagos D, Vart RJ, Gratrix F, Westrop SJ, Emuss V, Wong PP, Robey R, Imami N, Bower M, Gotch F, Boshoff C (2008) Toll-like receptor 4 mediates innate immunity to Kaposi sarcoma herpesvirus. Cell Host Microbe 4:470–483 [PubMed: 18996347]

195. Jacobs SR, Gregory SM, West JA, Wollish AC, Bennett CL, Blackbourn DJ, Heise MT, Damania B (2013) The viral interferon regulatory factors of kaposi's sarcoma-associated herpesvirus differ in their inhibition of interferon activation mediated by toll-like receptor 3. J Virol 87:798–806 [PubMed: 23115281]

196. Jacobs SR, Stopford CM, West JA, Bennett CL, Giffin L, Damania B (2015) Kaposi's Sarcoma-associated herpesvirus viral interferon regulatory factor 1 interacts with a member of the interferon-stimulated gene 15 pathway. J Virol 89:11572–11583 [PubMed: 26355087]

197. Bussey KA, Reimer E, Todt H, Denker B, Gallo A, Konrad A, Ottinger M, Adler H, Sturzl M, Brune W, Brinkmann MM (2014) The gammaherpesviruses Kaposi's sarcoma-associated herpesvirus and murine gammaherpesvirus 68 modulate the Toll-like receptor-induced proinflammatory cytokine response. J Virol 88:9245–9259 [PubMed: 24899179]

198. Gregory SM, Davis BK, West JA, Taxman DJ, Matsuzawa S, Reed JC, Ting JP, Damania B (2011) Discovery of a viral NLR homolog that inhibits the inflammasome. Science 331:330–334 [PubMed: 21252346]

199. Zhang G, Chan B, Samarina N, Abere B, Weidner-Glunde M, Buch A, Pich A, Brinkmann MM, Schulz TF (2016) Cytoplasmic isoforms of Kaposi sarcoma herpesvirus LANA recruit and antagonize the innate immune DNA sensor cGAS. Proc Natl Acad Sci U S A 113:E1034–43 [PubMed: 26811480]

200. Wu JJ, Li W, Shao Y, Avey D, Fu B, Gillen J, Hand T, Ma S, Liu X, Miley W, Konrad A, Neipel F, Sturzl M, Whitby D, Li H, Zhu F (2015) Inhibition of cGAS DNA Sensing by a Herpesvirus Virion Protein. Cell Host Microbe 18:333–344 [PubMed: 26320998]

201. Ma Z, Jacobs SR, West JA, Stopford C, Zhang Z, Davis Z, Barber GN, Glaunsinger BA, Dittmer DP, Damania B (2015) Modulation of the cGAS-STING DNA sensing pathway by gammaherpesviruses. Proc Natl Acad Sci U S A 112:E4306–15 [PubMed: 26199418]

202. Kerur N, Veettil MV, Sharma-Walia N, Bottero V, Sadagopan S, Otageri P, Chandran B (2011) IFI16 acts as a nuclear pathogen sensor to induce the inflammasome in response to Kaposi Sarcoma-associated herpesvirus infection. Cell Host Microbe 9:363–375 [PubMed: 21575908]

203. Roy A, Dutta D, Iqbal J, Pisano G, Gjyshi O, Ansari MA, Kumar B, Chandran B (2016) Nuclear innate immune DNA sensor IFI16 is degraded during lytic reactivation of Kaposi's Sarcoma-Associated Herpesvirus (KSHV): role of IFI16 in maintenance of KSHV Latency. J Virol 90:8822–8841 [PubMed: 27466416]

204. Areste C, Blackbourn DJ (2009) Modulation of the immune system by Kaposi's sarcoma-associated herpesvirus. Trends Microbiol 17:119–129 [PubMed: 19230674]

205. Lee MS, Jones T, Song DY, Jang JH, Jung JU, Gao SJ (2014) Exploitation of the complement system by oncogenic Kaposi's sarcoma-associated herpesvirus for cell survival and persistent infection. PLoS Pathog 10:e1004412 [PubMed: 25254972]

206. Thomas M, Wills M, Lehner PJ (2008) Natural killer cell evasion by an E3 ubiquitin ligase from Kaposi's sarcoma-associated herpesvirus. Biochem Soc Trans 36:459–463 [PubMed: 18481981]

207. Nachmani D, Stern-Ginossar N, Sarid R, Mandelboim O (2009) Diverse herpesvirus microRNAs target the stress-induced immune ligand MICB to escape recognition by natural killer cells. Cell Host Microbe 5:376–385 [PubMed: 19380116]

208. Madrid AS, Ganem D (2012) Kaposi's sarcoma-associated herpesvirus ORF54/dUTPase downregulates a ligand for the NK activating receptor NKp44. J Virol 86:8693–8704 [PubMed: 22674989]

209. Robey RC, Mletzko S, Bower M, Meys R, Boffito M, Nelson M, Bunker CB, Gotch FM (2011) Ex-vivo recognition of late-lytic CD8 epitopes specific for Kaposi's sarcoma-associated herpesvirus (KSHV) by HIV/KSHV-coinfected individuals. Viral Immunol 24:211–220 [PubMed: 21668362]

210. Bihl F, Mosam A, Henry LN, Chisholm JV 3rd, Dollard S, Gumbi P, Cassol E, Page T, Mueller N, Kiepiela P, Martin JN, Coovadia HM, Scadden DT, Brander C (2007) Kaposi's sarcoma-associated herpesvirus-specific immune reconstitution and antiviral effect of combined HAART/chemotherapy in HIV clade C-infected individuals with Kaposi's sarcoma. Aids 21:1245–1252 [PubMed: 17545700]

211. Miller G, Rigsby MO, Heston L, Grogan E, Sun R, Metroka C, Levy JA, Gao SJ, Chang Y, Moore P (1996) Antibodies to butyrate-inducible antigens of Kaposi's sarcoma-associated herpesvirus in patients with HIV-1 infection. N Engl J Med 334:1292–1297 [PubMed: 8609946]

212. Simpson GR, Schulz TF, Whitby D, Cook PM, Boshoff C, Rainbow L, Howard MR, Gao SJ, Bohenzky RA, Simmonds P, Lee C, de Ruiter A, Hatzakis A, Tedder RS, Weller IV, Weiss RA, Moore PS (1996) Prevalence of Kaposi's sarcoma associated herpesvirus infection measured by antibodies to recombinant capsid protein and latent immunofluorescence antigen. Lancet 348:1133–1138 [PubMed: 8888167]

213. Choi JK, Lee BS, Shim SN, Li M, Jung JU (2000) Identification of the novel K15 gene at the rightmost end of the Kaposi's sarcoma-associated herpesvirus genome. J Virol 74:436–446 [PubMed: 10590133]

214. Coscoy L, Ganem D (2001) A viral protein that selectively downregulates ICAM-1 and B7-2 and modulates T cell costimulation. J Clin Invest 107:1599–1606 [PubMed: 11413168]

215. Ishido S, Wang C, Lee BS, Cohen GB, Jung JU (2000) Downregulation of major histocompatibility complex class I molecules by Kaposi's sarcoma-associated herpesvirus K3 and K5 proteins. J Virol 74:5300–5309 [PubMed: 10799607]

216. Brulois K, Toth Z, Wong LY, Feng P, Gao SJ, Ensser A, Jung JU (2014) Kaposi's sarcoma-associated herpesvirus K3 and K5 ubiquitin E3 ligases have stage-specific immune evasion roles during lytic replication. J Virol 88:9335–9349 [PubMed: 24899205]

217. Brulois K, Jung JU (2014) Interplay between Kaposi's sarcoma-associated herpesvirus and the innate immune system. Cytokine Growth Factor Rev 25:597–609 [PubMed: 25037686]

218. Lagos D, Trotter MW, Vart RJ, Wang HW, Matthews NC, Hansen A, Flore O, Gotch F, Boshoff C (2007) Kaposi sarcoma herpesvirus-encoded vFLIP and vIRF1 regulate antigen presentation in lymphatic endothelial cells. Blood 109:1550–1558 [PubMed: 17047149]

219. Butler LM, Jeffery HC, Wheat RL, Long HM, Rae PC, Nash GB, Blackbourn DJ (2012) Kaposi's sarcoma-associated herpesvirus inhibits expression and function of endothelial cell major histocompatibility complex class II via suppressor of cytokine signaling 3. J Virol 86:7158–7166 [PubMed: 22532676]

220. Zuo J, Hislop AD, Leung CS, Sabbah S, Rowe M (2013) Kaposi's sarcoma-associated herpesvirus-encoded viral IRF3 modulates major histocompatibility complex class II (MHC-II) antigen presentation through MHC-II transactivator-dependent and -independent mechanisms: implications for oncogenesis. J Virol 87:5340–5350 [PubMed: 23449805]

221. Cirone M, Lucania G, Bergamo P, Trivedi P, Frati L, Faggioni A (2007) Human herpesvirus 8 (HHV-8) inhibits monocyte differentiation into dendritic cells and impairs their immunostimulatory activity. Immunol Lett 113:40–46 [PubMed: 17822781]

222. Gregory SM, Wang L, West JA, Dittmer DP, Damania B (2012) Latent Kaposi's sarcoma-associated herpesvirus infection of monocytes downregulates expression of adaptive immune response costimulatory receptors and proinflammatory cytokines. J Virol 86:3916–3923 [PubMed: 22278234]

223. Hong YK, Foreman K, Shin JW, Hirakawa S, Curry CL, Sage DR, Libermann T, Dezube BJ, Fingeroth JD, Detmar M (2004) Lymphatic reprogramming of blood vascular endothelium by Kaposi sarcoma-associated herpesvirus. Nat Genet 36:683–685 [PubMed: 15220917]

224. Wang HW, Trotter MW, Lagos D, Bourboulia D, Henderson S, Makinen T, Elliman S, Flanagan AM, Alitalo K, Boshoff C (2004) Kaposi sarcoma herpesvirus-induced cellular reprogramming contributes to the lymphatic endothelial gene expression in Kaposi's sarcoma. Nat Genet 36:687–693 [PubMed: 15220918]

225. Flore O, Rafii S, Ely S, O'Leary JJ, Hyjek EM, Cesarman E (1998) Transformation of primary human endothelial cells by Kaposi's sarcoma-associated herpesvirus. Nature 394:588–592 [PubMed: 9707121]

226. Wang L, Damania B (2008) Kaposi's sarcoma-associated herpesvirus confers a survival advantage to endothelial cells. Cancer Res 68:4640–4648 [PubMed: 18559509]

227. Mutlu AD, Cavallin LE, Vincent L, Chiozzini C, Eroles P, Duran EM, Asgari Z, Hooper AT, La Perle KM, Hilsher C, Gao SJ, Dittmer DP, Rafii S, Mesri EA (2007) In vivo-restricted and reversible malignancy induced by human herpesvirus-8 KSHV: a cell and animal model of virally induced Kaposi's sarcoma. Cancer Cell 11:245–258 [PubMed: 17349582]

228. Lee MS, Yuan H, Jeon H, Zhu Y, Yoo S, Shi S, Krueger B, Renne R, Lu C, Jung JU, Gao SJ (2016) Human mesenchymal stem cells of diverse origins support persistent infection with Kaposi's sarcoma-associated herpesvirus and manifest distinct angiogenic, invasive, and transforming phenotypes. MBio 7:e02109–15

229. Wu W, Vieira J, Fiore N, Banerjee P, Sieburg M, Rochford R, Harrington W Jr, Feuer G (2006) KSHV/HHV-8 infection of human hematopoietic progenitor (CD34+) cells: persistence of infection during hematopoiesis in vitro and in vivo. Blood 108:141–151 [PubMed: 16543476]

230. Di Bartolo DL, Cannon M, Liu YF, Renne R, Chadburn A, Boshoff C, Cesarman E (2008) KSHV LANA inhibits TGF-beta signaling through epigenetic silencing of the TGF-beta type II receptor. Blood 111:4731–4740 [PubMed: 18199825]

231. Santag S, Jager W, Karsten CB, Kati S, Pietrek M, Steinemann D, Sarek G, Ojala PM, Schulz TF (2013) Recruitment of the tumour suppressor protein p73 by Kaposi's sarcoma herpesvirus latent nuclear antigen contributes to the survival of primary effusion lymphoma cells. Oncogene 32:3676–3685 [PubMed: 22964633]

232. Friborg J Jr, Kong W, Hottiger MO, Nabel GJ (1999) p53 inhibition by the LANA protein of KSHV protects against cell death. Nature 402:889–894 [PubMed: 10622254]

233. Radkov SA, Kellam P, Boshoff C (2000) 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 6:1121–1127 [PubMed: 11017143]

234. Lu J, Verma SC, Murakami M, Cai Q, Kumar P, Xiao B, Robertson ES (2009) Latency-associated nuclear antigen of Kaposi's sarcoma-associated herpesvirus (KSHV) upregulates survivin expression in KSHV-Associated B-lymphoma cells and contributes to their proliferation. J Virol 83:7129–7141 [PubMed: 19439469]

235. Bubman D, Guasparri I, Cesarman E (2007) Deregulation of c-Myc in primary effusion lymphoma by Kaposi's sarcoma herpesvirus latency-associated nuclear antigen. Oncogene 26:4979–4986 [PubMed: 17310999]

236. Qin Z, Dai L, Slomiany MG, Toole BP, Parsons C (2010) Direct activation of emmprin and associated pathogenesis by an oncogenic herpesvirus. Cancer Res 70:3884–3889 [PubMed: 20406987]

237. Liu J, Martin HJ, Liao G, Hayward SD (2007) The Kaposi's sarcoma-associated herpesvirus LANA protein stabilizes and activates c-Myc. J Virol 81:10451–10459 [PubMed: 17634226]

238. Liang D, Hu H, Li S, Dong J, Wang X, Wang Y, He L, He Z, Gao Y, Gao SJ, Lan K (2014) Oncogenic herpesvirus KSHV Hijacks BMP-Smad1-Id signaling to promote tumorigenesis. PLoS Pathog 10:e1004253 [PubMed: 25010525]

239. Jha HC, Sun Z, Upadhyay SK, El-Naccache DW, Singh RK, Sahu SK, Robertson ES (2016) KSHV-Mediated Regulation of Par3 and SNAIL Contributes to B-Cell Proliferation. PLoS Pathog 12:e1005801 [PubMed: 27463802]

240. Zhu Y, Ramos da Silva S, He M, Liang Q, Lu C, Feng P, Jung JU, Gao SJ (2016) An oncogenic virus promotes cell survival and cellular transformation by suppressing glycolysis. PLoS Pathog 12:e1005648 [PubMed: 27187079]

241. Ballon G, Chen K, Perez R, Tam W, Cesarman E (2011) Kaposi's sarcoma herpesvirus (KSHV) vFLIP oncoprotein induces B cell transdifferentiation and tumorigenesis in mice. J Clin Invest 121:1141–1153 [PubMed: 21339646]

242. Moody R, Zhu Y, Huang Y, Cui X, Jones T, Bedolla R, Lei X, Bai Z, Gao SJ (2013) KSHV microRNAs mediate cellular transformation and tumorigenesis by redundantly targeting cell growth and survival pathways. PLoS Pathog 9:e1003857 [PubMed: 24385912]

243. Zhi H, Zahoor MA, Shudofsky AM, Giam CZ (2015) KSHV vCyclin counters the senescence/G1 arrest response triggered by NF-kappaB hyperactivation. Oncogene 34:496–505 [PubMed: 24469036]

244. Godden-Kent D, Talbot SJ, Boshoff C, Chang Y, Moore P, Weiss RA, Mittnacht S (1997) The cyclin encoded by Kaposi's sarcoma-associated herpesvirus stimulates cdk6 to phosphorylate the retinoblastoma protein and histone H1. J Virol 71:4193–4198 [PubMed: 9151805]

245. Swanton C, Mann DJ, Fleckenstein B, Neipel F, Peters G, Jones N (1997) Herpes viral cyclin/Cdk6 complexes evade inhibition by CDK inhibitor proteins. Nature 390:184–187 [PubMed: 9367157]

246. Verschuren EW, Klefstrom J, Evan GI, Jones N (2002) The oncogenic potential of Kaposi's sarcoma-associated herpesvirus cyclin is exposed by p53 loss in vitro and in vivo. Cancer Cell 2:229–241 [PubMed: 12242155]

247. Jones T, Ramos da Silva S, Bedolla R, Ye F, Zhou F, Gao SJ (2014) Viral cyclin promotes KSHV-induced cellular transformation and tumorigenesis by overriding contact inhibition. Cell Cycle 13:845–858 [PubMed: 24419204]

248. Seo T, Park J, Lee D, Hwang SG, Choe J (2001) Viral interferon regulatory factor 1 of Kaposi's sarcoma-associated herpesvirus binds to p53 and represses p53-dependent transcription and apoptosis. J Virol 75:6193–6198 [PubMed: 11390621]

249. Seo T, Park J, Choe J (2005) Kaposi's sarcoma-associated herpesvirus viral IFN regulatory factor 1 inhibits transforming growth factor-beta signaling. Cancer Res 65:1738–1747 [PubMed: 15753369]

250. Bais C, Santomasso B, Coso O, Arvanitakis L, Raaka EG, Gutkind JS, Asch AS, Cesarman E, Gershengorn MC, Mesri EA (1998) G-protein-coupled receptor of Kaposi's sarcoma-associated herpesvirus is a viral oncogene and angiogenesis activator. Nature 391:86–89 [PubMed: 9422510]

251. Yang TY, Chen SC, Leach MW, Manfra D, Homey B, Wiekowski M, Sullivan L, Jenh CH, Narula SK, Chensue SW, Lira SA (2000) Transgenic expression of the chemokine receptor encoded by

human herpesvirus 8 induces an angioproliferative disease resembling Kaposi's sarcoma. J Exp Med 191:445–454 [PubMed: 10662790]

252. Krause CJ, Popp O, Thirunarayanan N, Dittmar G, Lipp M, Muller G (2016) MicroRNA-34a promotes genomic instability by a broad suppression of genome maintenance mechanisms downstream of the oncogene KSHV-vGPCR. Oncotarget 7:10414–10432 [PubMed: 26871287]
253. Martin D, Galisteo R, Molinolo AA, Wetzker R, Hirsch E, Gutkind JS (2011) PI3Kgamma mediates kaposi's sarcoma-associated herpesvirus vGPCR-induced sarcomagenesis. Cancer Cell 19:805–813 [PubMed: 21665152]
254. Martin D, Nguyen Q, Molinolo A, Gutkind JS (2014) Accumulation of dephosphorylated 4EBP after mTOR inhibition with rapamycin is sufficient to disrupt paracrine transformation by the KSHV vGPCR oncogene. Oncogene 33:2405–2412 [PubMed: 23708663]
255. Wu J, Xu Y, Mo D, Huang P, Sun R, Huang L, Pan S, Xu J (2014) Kaposi's sarcoma-associated herpesvirus (KSHV) vIL-6 promotes cell proliferation and migration by upregulating DNMT1 via STAT3 activation. PLoS ONE 9:e93478 [PubMed: 24675762]
256. Hideshima T, Chauhan D, Teoh G, Raje N, Treon SP, Tai YT, Shima Y, Anderson KC (2000) Characterization of signaling cascades triggered by human interleukin-6 versus Kaposi's sarcoma-associated herpes virus-encoded viral interleukin 6. Clin Cancer Res 6:1180–1189 [PubMed: 10741750]
257. Chen D, Choi YB, Sandford G, Nicholas J (2009) Determinants of secretion and intracellular localization of human herpesvirus 8 interleukin-6. J Virol 83:6874–6882 [PubMed: 19386721]
258. Chen D, Cousins E, Sandford G, Nicholas J (2012) Human herpesvirus 8 viral interleukin-6 interacts with splice variant 2 of vitamin K epoxide reductase complex subunit 1. J Virol 86:1577–1588 [PubMed: 22130532]
259. Lee H, Veazey R, Williams K, Li M, Guo J, Neipel F, Fleckenstein B, Lackner A, Desrosiers RC, Jung JU (1998) Deregulation of cell growth by the K1 gene of Kaposi's sarcoma-associated herpesvirus. Nat Med 4:435–440 [PubMed: 9546789]
260. Tomlinson CC, Damania B (2004) The K1 protein of Kaposi's sarcoma-associated herpesvirus activates the Akt signaling pathway. J Virol 78:1918–1927 [PubMed: 14747556]
261. Anders PM, Zhang Z, Bhende PM, Giffin L, Damania B (2016) The KSHV K1 protein modulates AMPK function to enhance cell survival. PLoS Pathog 12:e1005985 [PubMed: 27829024]
262. Tolani B, Gopalakrishnan R, Punj V, Matta H, Chaudhary PM (2014) Targeting Myc in KSHV-associated primary effusion lymphoma with BET bromodomain inhibitors. Oncogene 33:2928–2937 [PubMed: 23792448]
263. Aoki Y, Feldman GM, Tosato G (2003) Inhibition of STAT3 signaling induces apoptosis and decreases survivin expression in primary effusion lymphoma. Blood 101:1535–1542 [PubMed: 12393476]
264. He M, Tan B, Vasan K, Yuan H, Cheng F, Ramos da Silva S, Lu C, Gao SJ (2017) SIRT1 and AMPK pathways are essential for the proliferation and survival of primary effusion lymphoma cells. J Pathol
265. He M, Yuan H, Tan B, Bai R, Kim HS, Bae S, Che L, Kim JS, Gao SJ (2016) SIRT1-mediated downregulation of p27Kip1 is essential for overcoming contact inhibition of Kaposi's sarcoma-associated herpesvirus transformed cells. Oncotarget 7:75698–75711 [PubMed: 27708228]
266. Bhatt S, Ashlock BM, Toomey NL, Diaz LA, Mesri EA, Lossos IS, Ramos JC (2013) Efficacious proteasome/HDAC inhibitor combination therapy for primary effusion lymphoma. J Clin Invest 123:2616–2628 [PubMed: 23635777]
267. Chaisuparat R, Hu J, Jham BC, Knight ZA, Shokat KM, Montaner S (2008) Dual inhibition of PI3Kalpha and mTOR as an alternative treatment for Kaposi's sarcoma. Cancer Res 68:8361–8368 [PubMed: 18922908]
268. Dai L, Trillo-Tinoco J, Cao Y, Bonstaff K, Doyle L, Del Valle L, Whitby D, Parsons C, Reiss K, Zabaleta J, Qin Z (2015) Targeting HGF/c-MET induces cell cycle arrest, DNA damage, and apoptosis for primary effusion lymphoma. Blood 126:2821–2831 [PubMed: 26531163]
269. Lam BQ, Dai L, Li L, Qiao J, Lin Z, Qin Z (2017) Molecular mechanisms of activating c-MET in KSHV+ primary effusion lymphoma. Oncotarget 8:18373–18380 [PubMed: 28407694]

270. Korniluk A, Koper O, Kemona H, Dymicka-Piekarska V (2017) From inflammation to cancer. Ir J Med Sci 186:57–62 [PubMed: 27156054]
271. Balkwill FR, Mantovani A (2012) Cancer-related inflammation: common themes and therapeutic opportunities. Semin Cancer Biol 22:33–40 [PubMed: 22210179]
272. Riva G, Barozzi P, Torelli G, Luppi M (2010) Immunological and inflammatory features of Kaposi's sarcoma and other Kaposi's sarcoma-associated herpesvirus/human herpesvirus 8-associated neoplasias. AIDS Rev 12:40–51 [PubMed: 20216909]
273. Guedes F, de Andrade HF Jr, Fernandes ER, Tuon FF, Brasil RA, Pagliari C, Duarte MI (2008) The effects of human herpesvirus 8 infection and interferon-gamma response in cutaneous lesions of Kaposi sarcoma differ among human immunodeficiency virus-infected and uninfected individuals. Br J Dermatol 159:839–846 [PubMed: 18644020]
274. Breuer-McHam JN, Ledbetter LS, Sarris AH, Duvic M (2000) Cytokine expression patterns distinguish HIV associated skin diseases. Exp Dermatol 9:341–350 [PubMed: 11016855]
275. Desnoyer A, Dupin N, Assoumou L, Carlotti A, Gaudin F, Deback C, Peytavin G, Marcelin AG, Boue F, Balabanian K, Pourcher V, group A. L. t. (2016) Expression pattern of the CXCL12/CXCR4-CXCR7 trio in Kaposi sarcoma skin lesions. Br J Dermatol 175:1251–1262 [PubMed: 27177037]
276. DiMaio TA, Gutierrez KD, Lagunoff M (2014) Kaposi's sarcoma-associated herpesvirus downregulates transforming growth factor beta2 to promote enhanced stability of capillary-like tube formation. J Virol 88:14301–14309 [PubMed: 25275137]
277. Douglas JL, Gustin JK, Moses AV, Dezube BJ, Pantanowitz L (2010) Kaposi's sarcoma pathogenesis: a triad of viral infection, oncogenesis and chronic inflammation. Transl Biomed 1 pii: 172 [PubMed: 23082307]
278. Dai L, Bratoeva M, Toole BP, Qin Z, Parsons C (2012) KSHV activation of VEGF secretion and invasion for endothelial cells is mediated through viral upregulation of emmprin-induced signal transduction. Int J Cancer 131:834–843 [PubMed: 21918972]
279. Wang X, He Z, Xia T, Li X, Liang D, Lin X, Wen H, Lan K (2014) Latency-associated nuclear antigen of Kaposi sarcoma-associated herpesvirus promotes angiogenesis through targeting notch signaling effector Hey1. Cancer Res 74:2026–2037 [PubMed: 24523441]
280. Cheng F, Pekkonen P, Laurinavicius S, Sugiyama N, Henderson S, Gunther T, Rantanen V, Kaivanto E, Aavikko M, Sarek G, Hautaniemi S, Biberfeld P, Aaltonen L, Grundhoff A, Boshoff C, Alitalo K, Lehti K, Ojala PM (2011) KSHV-initiated notch activation leads to membrane-type-1 matrix metalloproteinase-dependent lymphatic endothelial-to-mesenchymal transition. Cell Host Microbe 10:577–590 [PubMed: 22177562]
281. Zaldumbide A, Ossevoort M, Wiertz EJ, Hoeben RC (2007) In cis inhibition of antigen processing by the latency-associated nuclear antigen I of Kaposi sarcoma herpes virus. Mol Immunol 44:1352–1360 [PubMed: 16828498]
282. Thakker S, Purushothaman P, Gupta N, Challa S, Cai Q, Verma SC (2015) Kaposi's sarcoma-associated herpesvirus latency-associated nuclear antigen inhibits major histocompatibility complex class II expression by disrupting enhanceosome assembly through binding with the regulatory factor X complex. J Virol 89:5536–5556 [PubMed: 25740990]
283. Liu L, Eby MT, Rathore N, Sinha SK, Kumar A, Chaudhary PM (2002) The human herpes virus 8-encoded viral FLICE inhibitory protein physically associates with and persistently activates the Ikappa B kinase complex. J Biol Chem 277:13745–13751 [PubMed: 11830587]
284. Matta H, Chaudhary PM (2004) 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 101:9399–9404 [PubMed: 15190178]
285. Sharma-Walia N, Patel K, Chandran K, Marginean A, Bottero V, Kerur N, Paul AG (2012) COX-2/PGE2: molecular ambassadors of Kaposi's sarcoma-associated herpes virus oncoprotein-v-FLIP. Oncogenesis 1:e5 [PubMed: 23552603]
286. Guo Y, Li W, Qin J, Lu C, Fan W (2017) Kaposi's sarcoma-associated herpesvirus (KSHV)-encoded microRNAs promote matrix metalloproteinases (MMPs) expression and pro-angiogenic cytokine secretion in endothelial cells. J Med Virol 89:1274–1280 [PubMed: 28165144]

287. Breen EC (2007) VEGF in biological control. J Cell Biochem 102:1358–1367 [PubMed: 17979153]

288. Hu M, Wang C, Li W, Lu W, Bai Z, Qin D, Yan Q, Zhu J, Krueger BJ, Renne R, Gao SJ, Lu C (2015) A KSHV microRNA directly targets G protein-coupled receptor Kinase 2 to promote the migration and invasion of endothelial cells by inducing CXCR2 and activating AKT signaling. PLoS Pathog 11:e1005171 [PubMed: 26402907]

289. Li W, Jia X, Shen C, Zhang M, Xu J, Shang Y, Zhu K, Hu M, Yan Q, Qin D, Lee MS, Zhu J, Lu H, Krueger BJ, Renne R, Gao SJ, Lu C (2016) A KSHV microRNA enhances viral latency and induces angiogenesis by targeting GRK2 to activate the CXCR2/AKT pathway. Oncotarget 7:32286–32305 [PubMed: 27058419]

290. Li W, Yan Q, Ding X, Shen C, Hu M, Zhu Y, Qin D, Lu H, Krueger BJ, Renne R, Gao SJ, Lu C (2016) The SH3BGR/STAT3 pathway regulates cell migration and angiogenesis induced by a gammaherpesvirus microRNA. PLoS Pathog 12:e1005605 [PubMed: 27128969]

291. Li W, Hu M, Wang C, Lu H, Chen F, Xu J, Shang Y, Wang F, Qin J, Yan Q, Krueger BJ, Renne R, Gao SJ, Lu C (2017) A viral microRNA downregulates metastasis suppressor CD82 and induces cell invasion and angiogenesis by activating the c-Met signaling. Oncogene. 5 22 10.1038/onc.2017.139 . [Epub ahead of print]

292. Liu Y, Sun R, Lin X, Liang D, Deng Q, Lan K (2012) Kaposi's sarcoma-associated herpesvirus-encoded microRNA miR-K12-11 attenuates transforming growth factor beta signaling through suppression of SMAD5. J Virol 86:1372–1381 [PubMed: 22013049]

293. Samols MA, Skalsky RL, Maldonado AM, Riva A, Lopez MC, Baker HV, Renne R (2007) Identification of cellular genes targeted by KSHV-encoded microRNAs. PLoS Pathog 3:e65 [PubMed: 17500590]

294. Yoo J, Kang J, Lee HN, Aguilar B, Kafka D, Lee S, Choi I, Lee J, Ramu S, Haas J, Koh CJ, Hong YK (2010) Kaposin-B enhances the PROX1 mRNA stability during lymphatic reprogramming of vascular endothelial cells by Kaposi's sarcoma herpes virus. PLoS Pathog 6:e1001046 [PubMed: 20730087]

295. McCormick C, Ganem D (2005) The kaposin B protein of KSHV activates the p38/MK2 pathway and stabilizes cytokine mRNAs. Science 307:739–741 [PubMed: 15692053]

296. Chang HC, Hsieh TH, Lee YW, Tsai CF, Tsai YN, Cheng CC, Wang HW(2016) c-Myc and viral cofactor Kaposin B co-operate to elicit angiogenesis through modulating miRNome traits of endothelial cells. BMC Syst Biol 10(Suppl 1):1 [PubMed: 26817819]

297. Shin YC, Joo CH, Gack MU, Lee HR, Jung JU (2008) Kaposi's sarcoma-associated herpesvirus viral IFN regulatory factor 3 stabilizes hypoxia-inducible factor-1 alpha to induce vascular endothelial growth factor expression. Cancer Res 68:1751–1759 [PubMed: 18339855]

298. Brinkmann MM, Glenn M, Rainbow L, Kieser A, Henke-Gendo C, Schulz TF (2003) Activation of mitogen-activated protein kinase and NF-kappaB pathways by a Kaposi's sarcoma-associated herpesvirus K15 membrane protein. J Virol 77:9346–9358 [PubMed: 12915550]

299. Cho NH, Choi YK, Choi JK (2008) Multi-transmembrane protein K15 of Kaposi's sarcoma-associated herpesvirus targets Lyn kinase in the membrane raft and induces NFAT/AP1 activities. Exp Mol Med 40:565–573 [PubMed: 18985015]

300. Bala K, Bosco R, Gramolelli S, Haas DA, Kati S, Pietrek M, Havemeier A, Yakushko Y, Singh VV, Dittrich-Breiholz O, Kracht M, Schulz TF (2012) Kaposi's sarcoma herpesvirus K15 protein contributes to virus-induced angiogenesis by recruiting PLCgamma1 and activating NFAT1-dependent RCAN1 expression. PLoS Pathog 8:e1002927 [PubMed: 23028325]

301. Lee BS, Lee SH, Feng P, Chang H, Cho NH, Jung JU (2005) Characterization of the Kaposi's sarcoma-associated herpesvirus K1 signalosome. J Virol 79:12173–12184 [PubMed: 16160144]

302. Wang L, Wakisaka N, Tomlinson CC, DeWire SM, Krall S, Pagano JS, Damania B (2004) The Kaposi's sarcoma-associated herpesvirus (KSHV/HHV-8) K1 protein induces expression of angiogenic and invasion factors. Cancer Res 64:2774–2781 [PubMed: 15087393]

303. Bergers G, Brekken R, McMahon G, Vu TH, Itoh T, Tamaki K, Tanzawa K, Thorpe P, Itohara S, Werb Z, Hanahan D (2000) Matrix metalloproteinase-9 triggers the angiogenic switch during carcinogenesis. Nat Cell Biol 2:737–744 [PubMed: 11025665]

304. Yao S, Hu M, Hao T, Li W, Xue X, Xue M, Zhu X, Zhou F, Qin D, Yan Q, Zhu J, Gao SJ, Lu C (2015) MiRNA-891a-5p mediates HIV-1 Tat and KSHV Orf-K1 synergistic induction of angiogenesis by activating NF-kappaB signaling. Nucleic Acids Res 43:9362–9378 [PubMed: 26446987]

305. Xue M, Yao S, Hu M, Li W, Hao T, Zhou F, Zhu X, Lu H, Qin D, Yan Q, Zhu J, Gao SJ, Lu C (2014) HIV-1 Nef and KSHV oncogene K1 synergistically promote angiogenesis by inducing cellular miR-718 to regulate the PTEN/AKT/mTOR signaling pathway. Nucleic Acids Res 42:9862–9879 [PubMed: 25104021]

306. Mansouri M, Rose PP, Moses AV, Fruh K (2008) Remodeling of endothelial adherens junctions by Kaposi's sarcoma-associated herpesvirus. J Virol 82:9615–9628 [PubMed: 18667499]

307. Aoki Y, Jaffe ES, Chang Y, Jones K, Teruya-Feldstein J, Moore PS, Tosato G (1999) Angiogenesis and hematopoiesis induced by Kaposi's sarcoma-associated herpesvirus-encoded interleukin-6. Blood 93:4034–4043 [PubMed: 10361100]

308. Cannon M (2007) The KSHV and other human herpesviral G protein-coupled receptors. Curr Top Microbiol Immunol 312:137–156 [PubMed: 17089796]

309. de Munnik SM, Smit MJ, Leurs R, Vischer HF (2015) Modulation of cellular signaling by herpesvirus-encoded G protein-coupled receptors. Front Pharmacol 6:40 [PubMed: 25805993]

310. Pati S, Cavrois M, Guo HG, Foulke JS Jr, Kim J, Feldman RA, Reitz M (2001) Activation of NF-kappaB by the human herpesvirus 8 chemokine receptor ORF74: evidence for a paracrine model of Kaposi's sarcoma pathogenesis. J Virol 75:8660–8673 [PubMed: 11507211]

311. Choi YB, Nicholas J (2008) Autocrine and paracrine promotion of cell survival and virus replication by human herpesvirus 8 chemokines. J Virol 82:6501–6513 [PubMed: 18434408]

312. Stine JT, Wood C, Hill M, Epp A, Raport CJ, Schweickart VL, Endo Y, Sasaki T, Simmons G, Boshoff C, Clapham P, Chang Y, Moore P, Gray PW, Chantry D (2000) KSHV-encoded CC chemokine vMIP-III is a CCR4 agonist, stimulates angiogenesis, and selectively chemoattracts TH2 cells. Blood 95:1151–1157 [PubMed: 10666184]

313. Nicholas J (2010) Human herpesvirus 8-encoded cytokines. Future Virol 5:197–206 [PubMed: 20436945]

314. Szpakowska M, Chevigne A (2016) vCCL2/vMIP-II, the viral master KEYmokine. J Leukoc Biol 99:893–900 [PubMed: 26701133]

315. Delgado T, Carroll PA, Punjabi AS, Margineantu D, Hockenbery DM, Lagunoff M (2010) Induction of the Warburg effect by Kaposi's sarcoma herpesvirus is required for the maintenance of latently infected endothelial cells. Proc Natl Acad Sci U S A 107:10696–10701 [PubMed: 20498071]

316. Ma T, Patel H, Babapoor-Farrokhran S, Franklin R, Semenza GL, Sodhi A, Montaner S (2015) KSHV induces aerobic glycolysis and angiogenesis through HIF-1-dependent upregulation of pyruvate kinase 2 in Kaposi's sarcoma. Angiogenesis 18:477–488 [PubMed: 26092770]

317. Daye D, Wellen KE (2012) Metabolic reprogramming in cancer: unraveling the role of glutamine in tumorigenesis. Semin Cell Dev Biol 23:362–369 [PubMed: 22349059]

318. Jain M, Nilsson R, Sharma S, Madhusudhan N, Kitami T, Souza AL, Kafri R, Kirschner MW, Clish CB, Mootha VK (2012) Metabolite profiling identifies a key role for glycine in rapid cancer cell proliferation. Science 336:1040–1044 [PubMed: 22628656]

319. Sanchez EL, Carroll PA, Thalhofer AB, Lagunoff M (2015) Latent KSHV infected endothelial cells are glutamine addicted and require glutaminolysis for survival. PLoS Pathog 11:e1005052 [PubMed: 26197457]

320. Zhu Y, Li TT, Ramos da Silva S, Lee JJ, Lu C, Eoh HJ, Jung JU, Gao SJ (2017) A critical role of glutamine γ-nitrogen for nucleotide biosynthesis in cancer cells hijacked by an oncogenic virus mBio, submitted

321. Delgado T, Sanchez EL, Camarda R, Lagunoff M (2012) Global metabolic profiling of infection by an oncogenic virus: KSHV induces and requires lipogenesis for survival of latent infection. PLoS Pathog 8:e1002866 [PubMed: 22916018]

322. Sychev ZE, Hu A, DiMaio TA, Gitter A, Camp ND, Noble WS, Wolf-Yadlin A, Lagunoff M (2017) Integrated systems biology analysis of KSHV latent infection reveals viral induction and

reliance on peroxisome mediated lipid metabolism. PLoS Pathog 13:e1006256 [PubMed: 28257516]

323. Bhatt AP, Jacobs SR, Freemerman AJ, Makowski L, Rathmell JC, Dittmer DP, Damania B (2012) Dysregulation of fatty acid synthesis and glycolysis in non-Hodgkin lymphoma. Proc Natl Acad Sci U S A 109:11818–11823 [PubMed: 22752304]
324. Sanchez EL, Pulliam TH, Dimaio TA, Thalhofer AB, Delgado T, Lagunoff M (2017) Glycolysis, glutaminolysis, and fatty acid synthesis are required for distinct stages of Kaposi's sarcoma-associated herpesvirus lytic replication. J Virol 91: 4 28;91(10). pii: e02237–16. 10.1128/jvi.02237-16 . Print 2017 May 15 [PubMed: 28275189]
325. Cianfrocca M, Lee S, Von Roenn J, Tulpule A, Dezube BJ, Aboulafia DM, Ambinder RF, Lee JY, Krown SE, Sparano JA (2010) Randomized trial of paclitaxel versus pegylated liposomal doxorubicin for advanced human immunodeficiency virus-associated Kaposi sarcoma: evidence of symptom palliation from chemotherapy. Cancer 116:3969–3977 [PubMed: 20564162]
326. Pinzone MR, Berretta M, Cacopardo B, Nunnari G (2015) Epstein-barr virus- and Kaposi sarcoma-associated herpesvirus-related malignancies in the setting of human immunodeficiency virus infection. Semin Oncol 42:258–271 [PubMed: 25843730]
327. Roy D, Sin SH, Lucas A, Venkataramanan R, Wang L, Eason A, Chavakula V, Hilton IB, Tamburro KM, Damania B, Dittmer DP (2013) mTOR inhibitors block Kaposi sarcoma growth by inhibiting essential autocrine growth factors and tumor angiogenesis. Cancer Res 73:2235–2246 [PubMed: 23382046]
328. Sin SH, Roy D, Wang L, Staudt MR, Fakhari FD, Patel DD, Henry D, Harrington WJ Jr, Damania BA, Dittmer DP (2007) Rapamycin is efficacious against primary effusion lymphoma (PEL) cell lines in vivo by inhibiting autocrine signaling. Blood 109:2165–2173 [PubMed: 17082322]
329. Petre CE, Sin SH, Dittmer DP (2007) Functional p53 signaling in Kaposi's sarcoma-associated herpesvirus lymphomas: implications for therapy. J Virol 81:1912–1922 [PubMed: 17121789]
330. Sarek G, Kurki S, Enback J, Iotzova G, Haas J, Laakkonen P, Laiho M, Ojala PM (2007) Reactivation of the p53 pathway as a treatment modality for KSHV-induced lymphomas. J Clin Invest 117:1019–1028 [PubMed: 17364023]
331. Ye F, Lattif AA, Xie J, Weinberg A, Gao S (2012) Nutlin-3 induces apoptosis, disrupts viral latency and inhibits expression of angiopoietin-2 in Kaposi sarcoma tumor cells. Cell Cycle 11:1393–1399 [PubMed: 22421142]
332. Uldrick TS, Wyvill KM, Kumar P, O'Mahony D, Bernstein W, Aleman K, Polizzotto MN, Steinberg SM, Pittaluga S, Marshall V, Whitby D, Little RF, Yarchoan R (2012) Phase II study of bevacizumab in patients with HIV-associated Kaposi's sarcoma receiving antiretroviral therapy. J Clin Oncol 30:1476–1483 [PubMed: 22430271]
333. Koon HB, Krown SE, Lee JY, Honda K, Rapisuwon S, Wang Z, Aboulafia D, Reid EG, Rudek MA, Dezube BJ, Noy A (2014) Phase II trial of imatinib in AIDS-associated Kaposi's sarcoma: AIDS Malignancy Consortium Protocol 042. J Clin Oncol 32:402–408 [PubMed: 24378417]
334. van Rhee F, Wong RS, Munshi N, Rossi JF, Ke XY, Fossa A, Simpson D, Capra M, Liu T, Hsieh RK, Goh YT, Zhu J, Cho SG, Ren H, Cavet J, Bandekar R, Rothman M, Puchalski TA, Reddy M, van de Velde H, Vermeulen J, Casper C (2014) Siltuximab for multicentric Castleman's disease: a randomised, double-blind, placebo-controlled trial. Lancet Oncol 15:966–974 [PubMed: 25042199]
335. Dittmer DP, Damania B (2016) Kaposi sarcoma-associated herpesvirus: immunobiology, oncogenesis, and therapy. J Clin Invest 126:3165–3175 [PubMed: 27584730]
336. Bhatt AP, Bhende PM, Sin SH, Roy D, Dittmer DP, Damania B (2010) Dual inhibition of PI3 K and mTOR inhibits autocrine and paracrine proliferative loops in PI3 K/Akt/mTOR-addicted lymphomas. Blood 115:4455–4463 [PubMed: 20299510]