

Review

KSHV-Mediated Angiogenesis in Tumor Progression

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Abstract: Human herpesvirus 8 (HHV-8), also known as Kaposi's sarcoma-associated herpesvirus (KSHV), is a malignant human oncovirus belonging to the gamma herpesvirus family. HHV-8 is closely linked to the pathogenesis of Kaposi's sarcoma (KS) and two other B-cell lymphoproliferative diseases: primary effusion lymphoma (PEL) and a plasmablastic variant of multicentric Castleman's disease (MCD). KS is an invasive tumor of endothelial cells most commonly found in untreated HIV-AIDS or immuno-compromised individuals. KS tumors are highly vascularized and have abnormal, excessive neo-angiogenesis, inflammation, and proliferation of infected endothelial cells. KSHV directly induces angiogenesis in an autocrine and paracrine fashion through a complex interplay of various viral and cellular pro-angiogenic and inflammatory factors. KS is believed to originate due to a combination of KSHV's efficient strategies for evading host immune systems and several pro-angiogenic and pro-inflammatory stimuli. In addition, KSHV infection of endothelial cells produces a wide array of viral oncoproteins with transforming capabilities that regulate multiple host-signaling pathways involved in the activation of angiogenesis. It is likely that the cellular-signaling pathways of angiogenesis and lymph-angiogenesis modulate the rate of tumorigenesis induction by KSHV. This review summarizes the current knowledge on regulating KSHV-mediated angiogenesis by integrating the findings reported thus far on the roles of host and viral genes in oncogenesis, recent developments in cell-culture/animal-model systems, and various anti-angiogenic therapies for treating KSHV-related lymphoproliferative disorders.

Keywords: Kaposi's sarcoma-associated herpesvirus; KSHV; Kaposi's sarcoma; angiogenesis; lymphangiogenesis; oncogenesis; oncoproteins

1. Introduction

Kaposi's sarcoma-associated herpesvirus (KSHV), also called human herpesvirus 8 (HHV-8), is one of the most recently-discovered human oncogenic viruses and a major cause of aggressive, AIDS-defining malignancies worldwide [1]. KSHV is an enveloped virus containing a large (~165 kb) double-stranded (ds) DNA genome and belongs to the *Rhadinovirus* genus of the *Herpesviridae* family. KSHV is a γ 2-lymphotropic-oncogenic virus, classified together with Epstein-Barr virus (EBV), murine gammaherpesvirus-68 (MHV-68), and herpesvirus saimiri (HVS) (reviewed in [2]). KSHV was originally identified from Kaposi's sarcoma (KS) lesions from an AIDS patient using a representational difference analysis (RDA) technique [3]. Since its discovery in 1994, KSHV has been linked to the development of three neoplastic disorders, primarily KS, primary effusion lymphoma (PEL), or body cavity-based lymphoma (BCBL), and a plasmablastic variant of multicentric Castleman's disease (MCD) [4,5]. KSHV has also been shown to be associated with several other lymphomas, including germinotropic lymphoproliferative disease (GLD), multiple myeloma, angiosarcomas, malignant skin tumors and squamous cell carcinomas [6]. Recently, a new clinical KSHV-associated syndrome has

been identified, KSHV Inflammatory Cytokine Syndrome (KICS), which has clinical manifestations similar to KSHV-MCD [7]. KICS has been proposed to contribute to the inflammatory symptoms seen in patients infected with KS and PEL.

Similar to other herpesviruses, KSHV has a linear, double-stranded DNA genome, which is enclosed within a large icosahedral capsid, enveloped by an amorphous tegument layer consisting of several host and viral proteins and an outer glycoprotein-rich, lipid bilayer (reviewed in [8]). KSHV can infect various cell types [9,10] and exhibit either a lifelong, immunologically silent, latent infection or a transient, productive, lytic infection with distinct viral gene-expression profiles. During latent infection, the KSHV genome is maintained as a circular, extra-chromosomal episome, which replicates along with the host cell in a cell cycle-dependent manner with expression of a few viral genes, including latency-associated nuclear antigen (LANA, ORF73), viral cyclin (vCyclin, ORF72), viral FLIP (vFLIP, ORF71), and microRNAs, whose cooperative effects drive cell survival and proliferation (reviewed in [11]). The latent infection is the predominant infection state of KSHV, and in it the viral genome is maintained at 100–150 copies, which are tethered to the host chromosome. In contrast, during the lytic phase, the virus reactivates from latency leading to the production of infectious virions. Upon reactivation, a full repertoire of lytic viral genes, including ORF50, ORF57, ORF59, K8, ORF40, ORF6, ORF9, viral interleukin-6 (vIL-6, ORFK2), viral G protein-coupled receptor (vGPCR, ORF74), and viral chemokines (vCCL-I/ORFK6 and vCCL-II/ORFK4), are expressed in a temporally-regulated manner [12–14]. KSHV-encoded lytic genes are well documented to play a significant role in the secretion of multiple paracrine factors, including cytokines and growth factors, vascular endothelial growth factor (VEGF), interleukin-6 (IL-6), interleukin-8 (IL-8), platelet-derived growth factor (PDGF), fibroblast growth factor 2 (FGF2), and matrix metalloproteinases (MMPs), which induce angiogenesis, lymphatic reprogramming, and inflammatory lesions in uninfected and latently-infected cells. [15]. Both the latent and lytic gene transcription programs of KSHV are proposed to drive tumor progression.

Infection of endothelial cells with KSHV plays an important role in viral dissemination and paracrine induction of angiogenesis in KS lesions. KSHV-infected endothelial cells share the characteristics of transformed endothelial cells, including cell proliferation, chemotactic migration, and invasion [16,17]. Furthermore, KSHV infection can upregulate various cellular signaling pathways to increase endothelial cell proliferation and vascular permeability during angiogenesis and vasculogenesis [18]. Therefore, to control KSHV infection and formulate novel treatment strategies for KSHV-associated diseases, it is very important to elucidate the molecular biology of the cellular and viral factors implicated in KSHV-induced oncogenesis. Inhibitors targeting the mechanisms of KSHV-regulated cancer angiogenesis are thought to be effective therapeutic strategies for treating KSHV-associated malignancies.

2. KSHV-Associated Human Malignancies

2.1. Kaposi's Sarcoma (KS)

KSHV is the etiological agent of KS, a highly angiogenic endothelial cell tumor, most commonly seen in sub-Saharan Africa and in immune-deficient patients worldwide [19]. The most common KS tumors have spindle-shaped cells infected with KSHV and are clinically characterized by dark red, brown, or purple patches or plaques found cutaneously, mucosally, or viscerally [20]. These endothelial cells of KS tumors are highly proliferative, and the tumors have increased infiltration of inflammatory cells [21,22]. Several studies have shown that the elongated spindle cells of KS tumors sometimes express vascular endothelial cell markers, including CD31, CD34, and CD36 [23,24]. Recent data suggest that KS spindle cells closely resemble lymphatic endothelial cells (LECs) in that they express LYVE-1, VEGF-R3, and podoplanin markers of the lymphatic endothelium, making it difficult to identify the precursor cell type [25,26]. KSHV has been reported to induce c-kit gene expression in dermal microvascular endothelial (DMVEC) cells, thereby transforming them from a cobblestone-like monolayer to KS spindle cells [27,28].

KSHV is required for the development of KS and nearly all KS lesions harbor KSHV viral DNA in the latent phase, although a portion of infected cells in these lesions undergo lytic reactivation, which is believed to play an essential role in tumorigenesis [29]. The role of KSHV in KS development is complex and involves both latent and lytic genes, many of which are pirated versions of cellular genes (reviewed in [30]). KSHV has been identified in all four histologically indistinguishable, but different, epidemiological variants of KS, including Classical KS, Endemic KS, Iatrogenic/organ-transplant KS, and Epidemic AIDS-related KS (reviewed in [31]). Classic KS (the indolent form) usually presents as lesions in the lower and upper extremities without the involvements of lymph nodes and internal organs and affects elderly individuals of Mediterranean or Ashkenazi origin [32,33]. Endemic KS affects sub-Saharan regions and can be indolent or aggressive. Organ transplant-related KS is a relatively indolent, chronic condition with a rapidly progressing course that involves the lymph nodes, mucosa, and inner organs [34]. AIDS/HIV-related KS is the most frequent and aggressive form, indicating that HIV is a potent co-factor for KSHV tumorigenesis [34,35].

2.2. Primary Effusion Lymphoma (PEL)

PEL, or body cavity-based lymphomas (BCBL) is a high-grade, B-cell malignancy, an aggressive form of non-Hodgkin's B-cell lymphoma closely linked to KSHV infection [36]. PEL is often characterized as a lymphomatous effusion tumor present in various body cavities, including the pleurum, pericardium, and peritoneum [37]. Gene expression analyses of PEL cells has indicated the presence of the KSHV genome with a latent profile [38]. Studies have found all PEL cells to be KSHV-positive and nearly 70%–80% of them are also co-infected with EBV [39–41]. Consistent growth of PEL cell lines in culture and easy induction to release infectious KSHV virions have made them a valuable in vitro infection model for understanding cellular and molecular mechanisms of KSHV-induced oncogenesis, although the contribution of KSHV to B-cell malignancy still remains a clinical challenge [40].

2.3. Multicentric Castleman's Disease (MCD)

MCD, also called multicentric angiofollicular hyperplasia, is a rare, polyclonal, remitting-relapsing, B-cell lymphoproliferative disease, characterized by vascular proliferation of the germinal centers of the lymph nodes [42]. KSHV has been associated with the plasmablastic variant of MCD, and these lesions harbor the virus in both latent and lytic forms [43]. KS and MCD may occur together and are most commonly observed in immuno-compromised HIV patients and transplant recipients. MCD can also be found in association with B-cell lymphomas, including PEL and Hodgkin's lymphomas [44]. However, MCD usually does not co-occur with EBV, unlike PEL, and is driven by deregulated expression of cellular and viral cytokines, interleukin-6 (IL-6), and interleukin-10 (IL-10) [45]. In addition, expression of vFLIP, vGPCR, and Kaposin B can increase the expression of cytokines and VEGF in KS, thereby directly contributing to angioproliferation [43].

3. KSHV-Mediated Angiogenesis

Angiogenesis is defined as the process by which new blood vessels are formed from the pre-existing blood vessels in response to numerous mechanical, chemical, and inflammatory stimuli, enhancing tumor survival and progression [46]. Tumor growth and metastasis depend on angiogenesis and lymphangiogenesis. Angiogenesis is an important factor in the progression of cancer, as tumor cells are dependent on neovascularization for oxygen and nutrients to sustain their growth [47]. Angiogenesis is regulated through the balance of pro-angiogenic and anti-angiogenic factors, and these pro-angiogenic factors can be released by a variety of cells, including endothelial cells, monocytes, and tumor cells [48]. During tumor growth, excessive release of angiogenic cytokines and growth factors induces an "angiogenic switch" which stimulates the quiescent, non-proliferating, nearby endothelial cells to grow and promote tumor progression [16].

Accumulating evidence suggests that KSHV infection can directly induce tumorigenesis through the complex interplay of several viral, cellular angiogenic, and inflammatory markers [49]. KSHV-induced angiogenesis is microscopically visible even during the early stages of KS as leaky, poorly-organized, newly-developed vessels that result in red or purple lesions [50]. Histologically, KS tumors are characterized by abnormal differentiation of endothelial cells into spindle cells, erythrocyte leakage, and vascular spaces, resulting in aberrant vascular structures [50,51]. In cultured endothelial cells, KS infection readily induces angiogenic phenotypes via an elevated secretion of pro-angiogenic factors, including VEGF, IL-6, IL-8, MMPs, Ang2, and Ephrin B2 [52]. In addition, KSHV-infected endothelial cells grown on Matrigel have been shown to form tubules without any external growth factors [52,53]. Furthermore, KSHV-encoded latent and lytic proteins are known to synergistically modulate cellular autocrine and paracrine mechanisms, which contribute to the progression of KSHV-mediated tumorigenesis (Figure 1).

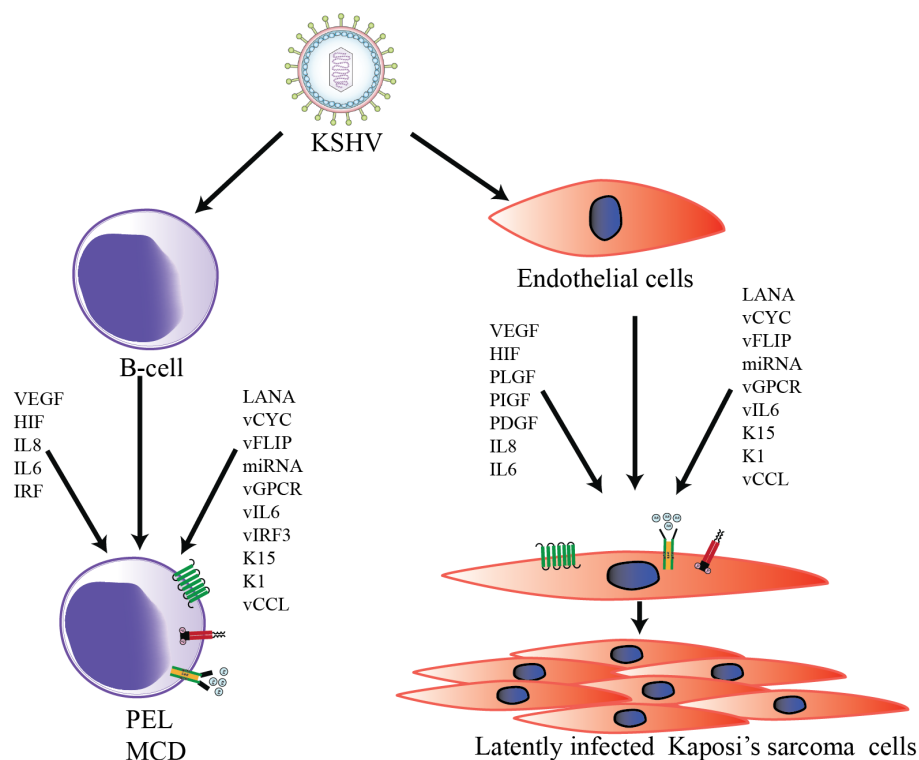


Figure 1. Schematic representation of Kaposi's sarcoma-associated herpesvirus (KSHV)-induced transformation of B-cells and endothelial cells. KSHV infection activates the expression of multiple viral as well as cellular autocrine and paracrine factors to modulate numerous signaling pathways in order to promote KSHV-mediated angiogenesis.

3.1. Cellular Factors

Cellular hallmarks of KSHV-mediated angiogenesis, including cellular cytokines, VEGF, and IL-6, are known to readily interact with their corresponding receptors to trigger endothelial cell proliferation [54]. The vIL-6 has been shown to upregulate VEGF expression and angiogenesis in experimental models [55]. Many KSHV latent and lytic proteins play an integral role in inducing angiogenesis and vasculogenesis, [56,57] by activating VEGF and VEGF-R2 [13,58]. It has been hypothesized that upregulation of VEGF during KSHV infection may contribute to a paracrine feedback loop for persistent cellular proliferation and angiogenesis [59,60].

VEGF is an inducer of angiogenesis [61] because it plays a crucial role in vascular permeability, proliferation, and survival of newly-formed vasculature. VEGF-A is a mitogen in endothelial cells in combination with VEGF-R1 and VEGF-R2 [62]. The spindle cells of KS lesions seem to harbor

VEGF-A, which is upregulated through inflammatory cytokines in KS lesions [63]. KSHV-positive PEL cell lines produce VEGF-A and, interestingly, it has been reported that capillary morphogenesis in certain endothelial cells can be easily induced if they are treated with conditioned media from these angiogenic cell lines [58,64,65]. In many instances, infection of endothelial cells with KSHV induces angiogenesis, as evidenced by high levels of VEGF-A expression following de novo infection [66–68].

In general, hypoxia-inducible factor 1-alpha (HIF-1 α) is highly unstable in the presence of oxygen, whereas its stability increases in hypoxic tumors. This allows HIF-1 α to trigger the transcription of several genes, including VEGF-A [69]. The function of hypoxia-inducible factors (HIF) is maintained by post-translational modification and stabilization of HIF-1 α and hypoxia-inducible factor 1-beta (HIF-1 β) proteins [70]. The mRNA of HIF-1 α possesses an internal ribosomal entry site that permits translation only under hypoxic conditions [71]. Therefore, KSHV targets HIF-1 α for its own advantage, as demonstrated by the augmented expression and stability of HIF-1 α in KSHV-infected endothelial cells [72]. The interferon response factor (vIRF-3) encoded by KSHV stabilizes HIF-1 α and increases VEGF-A expression [73]. In addition, KSHV manipulates the host glycoproteins initiating the ensuing angiogenic pathways, as observed in the role played by extracellular matrix metalloproteinase inducer (EMMPRIN), a membrane-associated glycoprotein, which increases the expression of VEGF-A during the infection of endothelial cells with KSHV, leading to cellular invasiveness by regulating PI3 kinase and mitogen-activated protein kinases (MAPK) pathways [17,74]. In the context of viral glycoproteins, the expressions of K8.1 and gB have been depicted in latently infected BCBL-1 cells, culminating in VEGF-A expression [65]. Transfection of siRNAs against glycoprotein gB and K8.1 or treatment of these targets with neutralizing antibodies has shown a significant reduction in VEGF-A production.

The sprouting of new blood vessels, remodeling of vasculature, and stimulation of angiogenic factors is governed by many signaling molecules that hold significant juxtapositions within the complex web of signaling pathways. For example, the expression of VEGF receptor is regulated by the PI3K pathway [75]. The heterodimer of PI3K, which comprises a catalytic (p110) and a regulatory subunit (p85), when activated, phosphorylates the effector molecule, AKT, at serine and threonine residues [54,76] stimulating the mammalian target of rapamycin (mTOR) pathway [77,78], which is critical for cell proliferation, gene transcription, protein synthesis, and cell survival [79–81], all of which indirectly support angiogenesis. While activating mTOR, AKT adapts various mechanisms, one of which is regulating adenosine triphosphate (ATP) at cellular levels [82]. This inactivates AMPK and Tuberous Sclerosis Complex 2 (TSC-2), and promotes angiogenic pathways. KSHV targets AMPK by suppressing it through the activation of the PI3K/AKT/mTOR pathway, which provides a survival advantage to endothelial cells [68]. In fact, this pathway is critical to the lytic and latent phases of KSHV, and viral proteins have been found to activate this pathway, individually, in both endothelial and B-cells. In addition, activated AKT and mTOR kinases have been identified in both KS and PEL cell lines [83–85]. Another pathway that has become significant in the past few decades is the Notch signaling pathway [86]. The downstream effectors of Notch signaling, namely Hey and Hes, have been found to be augmented in KSHV-infected cells [87]. Although earlier studies assumed Notch signaling to be associated with KSHV angiogenesis, its role in tumor growth has now been proven based on the significance of Hey-1 to the development of embryonic vasculatures [88,89]. Through Notch signaling, Hey-1 regulates bone morphogenetic proteins (BMPs), which are active participants in angiogenesis [90,91]. In addition, Hey-1 is highly expressed in KSHV tumor lesions compared to normal tissues [92]. In fact, it has been observed that LANA controls the angiogenic potential of this oncogene by preventing degradation of and stabilizing Hey-1 to cause angiogenesis via the formation of new blood vessels [87].

Among the tumor-suppressor pathways inhibited by KSHV, the Hippo pathway deserves a special mention. This pathway is evolutionarily conserved and comprises a complex network of molecules, primarily LATS1 and 2 kinases [93]. Activated kinases phosphorylate and inhibit Yes-associated protein (YAP) and its closed paralog TAZ (WWTR1) transcription co-activators, which leads to apoptosis and cell suppression [94]. The KSHV virus activates YAP/TAZ (homologous oncoproteins) by inhibiting the Hippo tumor-suppressor pathway kinases, LATS 1 and 2. This inhibition of the Hippo

pathway through vGPCR has been shown to be responsible for cell proliferation and tumorigenesis, in a xenograft mouse model [93].

Another interesting cellular proteins are MMPs, a group of enzymes that proteolytically degrades extracellular matrix (ECM) and contribute to angiogenesis by remodeling the ECM during tumor growth, angiogenesis, invasion, and metastasis [95]. KS tumors display an elevated expression of MMP-1, -2, -3, -9, and -19 [96,97], and their possible significance in KS pathology has been indicated by the evaluation of the MMP inhibitor COL-3 in the treatment of AIDS-related KS [98]. The KSHV protein K1 enhances the expression of MMP-9, which in turn directly regulates angiogenesis and tumor progression [60,99]. Analysis of KSHV-infected endothelial cells has indicated an elevated expression of MMP-1, -2, and -9, suggesting their possible role in ECM invasion [52]. Furthermore, it has been shown that KSHV LANA directly activates MMPs by upregulating EMMPRIN [74]. Angiopoietins are another significant family of endothelium-specific angiogenic factors that contribute to KSHV-mediated angiogenesis [100]. The angiopoietin family of VGFs includes, angiopoietin-1, -2, -3, and -4. Angiopoietin-1 (Ang-1/ANGPT-1) directly associates with the Tie-2 receptor tyrosine kinase and upregulates VEGF expression to promote endothelial cell proliferation and blood vessels stabilization. In contrast, angiopoietin-2 (Ang-2) is an antagonist of Tie-2 and destabilizes existing blood vessels [101,102]. Ang-1 is ubiquitously expressed in endothelial cells, whereas Ang-2 has been found to be upregulated at the sites of vascular remodeling [25,100,102,103]. Recently, a study from Keiji Ueda's group reported that DNA binding factors, including octamer-binding transcription factor (OCT1), play a key role in the upregulation of ANGPT-1 transcriptional activity in PEL cells [104], further indicating that cellular micro environments created by KSHV infection are most probably due to the upregulation of ANGPT-1 expression and may directly contribute to the disease progression in AIDS patients with PEL [104].

Tumor cells often induce angiogenesis by stabilizing HIFs, which are the transcription factors that interact with promoters containing hypoxia response elements (HREs). Interestingly, the key players in angiogenesis, VEGF and VEGF-R1, have been shown to contain HRE [105]. In addition, several viral proteins, including LANA, vIRF3, and vGPCR, can upregulate HIF expression [73,106,107], thereby increasing the levels of HIF angiogenic growth factors and cytokines (VEGF, PDGF, TGF α , TGF β , ANGPT-2, and ANGPTL-4) [106,108]. Additionally, it has been reported that HIF-dependent increases in pyruvate kinase M2 (PKM2) expression, and its upregulation, contribute to angiogenic phenotypes in KS [109]. Activation of both MAPK and p38 kinases that are dependent on KSHV GPCRs leads to subsequent phosphorylation and activation of HIF-1 α , which might be considered a plausible mechanism for vGPCR's induction by VEGF [72,107]. Moreover, KSHV-induced inflammatory processes are likely to play key roles in KS angiogenesis. Elevated expression of cyclooxygenase-2 (COX-2) has been found in KSHV-infected primary endothelial cells, and KS tissues have been reported to play a pivotal role in creating tumor microenvironments during de novo infection [110,111]. KSHV-encoded vFLIP and K15 have been shown to contribute to COX-2-mediated secretion of cellular chemokines and pro-angiogenic factors (IGF1, PDGF, IL14, MCSF, GM-CSF, VEGF-A and -C, angiogenin, oncostatin M, and TGF β 1) [49,111]. Overall, KSHV-induced pro-inflammatory cytokines and angiogenic factors might have evolved to create a tumor microenvironment favorable to viral genome maintenance and oncogenesis [49].

Infection of lymphatic endothelial cells with KSHV has been shown to result in the activation of PI3K/AKT/mTOR signaling pathways mediated through KSHV-encoded lytic proteins, namely, K1, vGPCR, and vIL-6 [112–114]. Similarly, KSHV infection in latently-infected PEL cells has demonstrated that PEL cell proliferation and pathogenesis are tightly regulated by a constitutive activation of transcription factor, signal transducer and activator of transcription 6 (STAT6) due to secretion of interleukin-13 (IL-13), downregulation of SH2-containing phosphatase-1 (SHP1), and phosphorylation of Janus kinase inhibitors 1 and 2 (JAK-1/JAK-2) tyrosine kinases [115]. KSHV GPCRs are known to modulate several downstream signaling cascades, including the nuclear factor of activated T-cells (NFAT) pathway. It has been suggested that viral GPCRs promote tumorigenesis by targeting sarcoplasmic reticulum calcium ATPase (SERCA) to elevate cytosolic calcium and

induce constitutive activation of the NFAT pathway [116]. Likewise, cellular transforming growth factor-beta 2 (TGF- β 2), a cytokine related to TGF- β 1, is known to inhibit angiogenesis [117]. In KS tumors and cultured endothelial cells, latent KSHV infection markedly downregulates TGF- β 2, but not TGF- β 1 mRNA, and induces angiogenic phenotypes, including an enhanced stabilization of capillary-like tube formation [16]. In addition, KSHV infection in cultured cells upregulates enhancer of zeste homolog 2 (EZH2) expression, which is essential for the induction of Ephrin-B2, an essential pro-angiogenic factor that promotes endothelial cell tubule formation [53]. Various other important cellular angiogenic proteins, including IL-1 β , FGF-2, HO-1, and PDGF-R β , are also highly expressed in KS lesions [118,119].

Recently, for the first time, the functional role of cholesteryl esters (CEs) was demonstrated during the latent and lytic phases of KSHV infection [120]. CEs and triglycerides are common components of lipid droplets found in PEL and non-viral lymphoma cells and seem to be closely linked to the angiogenic properties of the infected cells. These findings suggested that CE metabolism significantly contributes to neo-angiogenesis and reprogramming of KSHV-infected cells and plays a key role in the high metastatic potential of derived tumors [120]. Another recent study has shown that expression of tumor suppressor gene, PDZ and LIM domain protein-2, (PDLIM2) is repressed in KSHV-transformed human umbilical vascular endothelial cells (HUVEC) cells and KSHV-associated cancer cells [121]. In addition, PDLIM2 repression by KSHV is essential for the activation of nuclear factor κ B (NF- κ B) and signal transducer and activator of transcription 3 (STAT3), for subsequent cellular proliferation and maintenance [121]. Similarly, yet another study has shown that guanine exchange factor switch-associated protein 70 (SWAP70) is crucial for Rac-activation by vGPCR, vGPCR-mediated endothelial tube formation, and endothelial sprouting in vitro [122].

3.2. Viral Factors

In infected cells, KSHV can display both the latent and lytic phases of its life cycle [123]. The latent state is considered to be an immune-silent phase, with expression of a limited number of genes needed for episomal maintenance. In contrast, the lytic phase is characterized by the expression of all of the viral proteins. The switch between latent and lytic reactivation is a crucial step in KS pathogenesis [124]. Several KSHV-encoded latent and lytic oncoproteins, including LANA, vCYC, vFLIP, miRNA, K15, KaposinB, K1, K5, vIL-6, vGPCR, vIRF3, vMIPs, and vCCLs, are known to contribute to KSHV-induced aberrant angiogenesis [49]. Table 1 lists some of the important KSHV-encoded proteins and their possible role in KSHV-mediated angiogenesis.

LANA: LANA, the major latency-associated protein expressed in latently-infected PEL cell lines, has been shown to significantly inhibit p53, the cell cycle checkpoint protein and tumor suppressor [126,174]. LANA also interacts with the G1-S checkpoint proteins, pRB and GSK3 β , and modulates G1-S transition [175]. In addition, LANA increases the longevity of primary endothelial cells in culture and makes them less susceptible to apoptosis [127]. LANA has been reported to stabilize and activate the c-Myc oncogene, thereby affecting Myc phosphorylation, stability, transcriptional activity, and apoptotic functions [128,176]. Interaction of LANA with angiogenin (ANG), a multifunctional angiogenic protein, and annexin A2 has been identified in both latently-infected telomerase-immortalized human microvascular endothelium (TIME) and BCBL-1 cells. [177,178]. Upon KSHV infection, LANA has been shown to upregulate the expression of EMMPRIN, a modulator of metastasis and angiogenesis, in primary human fibroblast and endothelial cells [110,179]. Upregulation of EMMPRIN expression induces secretion of IL-6 and VEGF and enhances angiogenesis [17,74]. LANA also stabilizes the Notch effector Hey-1, thereby repressing the expression of Prox-1, a key player in the differentiation of lymphatic endothelial cells [92]. Furthermore, the activation of PDGFR β , expressed in KS lesions through Notch signaling contributes to the invasive properties of KSHV tumors [51,87,180]. KSHV-encoded LANA also has the potency to inhibit antigen presentation through its acidic central-repeat domain [181,182]. In fact, LANA inhibits immune pathways pertaining to IFN and TNF- α signaling and MHC-I peptide presentation [183–185]. In addition, LANA suppresses MHC-II gene expression by interacting with RFX proteins and

barring the recruitment of the class II trans-activator CIITA to the site of the MHC-II promoter [186]. Although it is quite apparent that KSHV diminishes antigen presentation, it should still be noted that KSHV also reduces the expression of cell markers, including CD80, CD86, CD1a, and CD83, on the antigen-presenting cells (APCs) [187]. LANA has been reported as being involved in the stability of HIF-1 α by (1) inducing the degradation of its suppressors, the von Hippel–Lindau protein and p53 [188]; and (2) interacting with HIF-1 α [189].

Table 1. Kaposi’s sarcoma-associated herpesvirus (KSHV)-encoded proteins and their role in KSHV-mediated angiogenesis.

KSHV Gene	KSHV Protein	Function	Reference
LANA	Latency Associated Nuclear Antigen	Apart from KSHV genome persistence, it inhibits p53, pRB and extends the lifespan of latently infected cells	[125–129]
vCYC	Homologue of cellular cyclin D	Primarily regulates cell cycle and promotes oncogene-induced senescence	[130–134]
vFLIP	Homologue of FLICE inhibitory protein	Regulates activation of NF- κ B and apoptosis. Additionally may contribute to PEL survival and spindle cell formation	[53,135–138]
miRNA	Micro RNAs	Contributes to B cell expansion and transformation of rat mesenchymal precursor cells. Downregulates TGF β signaling and MAF transcription factor. Contributes to cell proliferation and angiogenesis	[139–143]
K15	Viral membrane protein	Induce cell proliferation and angiogenesis. Activates cellular signaling pathways to induces various pro-survival and paracrine-mediated pro-angiogenic cellular cytokines and chemokines, including IL6, IL8, CXCL3, and Cox2	[144–148]
Kaposin B	Kaposin	Regulates cell signaling and reprogramming of vascular endothelial cells	[149–152]
K1	Variable ITAM-Containing Protein (VIP)	Activates cellular signaling pathways and induces angiogenesis	[60,113,146,153–155]
K5	Modulator of immune recognition (MIR2)	Viral E3 ligases capable of ubiquitinating MHC-I, ICAM-1, B7-2, Tetherin (CD317/BST2)	[156–159]
vIL6	Viral Interleukin-6	Homologues of cellular IL-6. Activate JAK/STAT, MAPK, and PI3K/Akt signaling to induce VEGF pathways to regulate B-cell proliferation	[55,160–163]
vGPCR	Viral G-protein-coupled receptor (vGPCR)	Homologue of cellular IL-8 receptor. vGPCR activates cellular signaling and induce secretion of proinflammatory cytokines and angiogenic growth factors contributing to angioproliferative tumors	[107,112,164–167]
vIRF3	Viral interferon regulatory factor-3	Homologues of cellular interferon: Inhibitor of IFN1, p53, NF κ B RelA, and p300. Activates HIF-1 α and VEGF	[73,168–171]
vCCL	Viral CC-Chemokine Ligands (vCCLs)	Homologues of cellular chemokines: viral CC-chemokine ligand 1 (vCCL1, (vMIP1), vCCL2 (vMIP2), and vCCL3 (vMIP3), respectively. Modulates signaling through chemokine receptors to promote cell proliferation and angiogenesis	[56,57,172,173]
Glycoprotein B	Glycoprotein	Activates VEGF secretion	[17,74]
K8.1	Glycoprotein	Activates VEGF secretion	[65,74]

vCYC: vCYC, a KSHV-encoded viral homologue of cellular cyclin D [112,190] also contributes to the abnormal characteristics of KS spindle cells [190] and proliferation in PEL cells [137,191]. KSHV-encoded vCYC is expressed together with another latent protein, vFLIP, from a bicistronic mRNA [190,192,193] without the physiological inhibition of cyclins by Cip/Kip or INK4 proteins [190,192,194]. Silencing vCYC or vFLIP by shRNA/siRNA has been shown to induce apoptosis in PEL cells [137]. vCYC, together with the cellular cyclin-dependent kinase CDK6, mediates the phosphorylation of CDC6 and Rb, increases DNA synthesis and triggers progression toward the S phase of the cell cycle [195,196].

vFLIP: Herpesviral FLICE Inhibitory Protein (vFLIP), encoded by KSHV ORF K13, is structurally related to the death effector domain (DED) and protects against apoptosis induced by Fas/CD95 and TNF receptors [197–199]. It has been reported that KSHV-encoded vFLIP induces NF- κ B signaling and suppresses Fas-induced apoptosis, suggesting that vFLIP functions primarily by activating classical and alternative NF- κ B pathways [200–202]. Thus, these studies clearly demonstrate that vFLIP plays an important role in maintaining long-term latency and has the potential to induce pro-inflammatory and angiogenic cytokines, including IL-6 and IL-8.

miRNA: KSHV encodes 12 microRNAs, the majority of which are located between the latently-expressed ORFs 71 and K12 gene in the genome. In addition, many of them have been shown to contribute to KSHV-mediated angiogenesis [203–206]. All 12 KSHV miRNAs are oriented “in sense” with ORFs 71 and K12 and are expressed primarily during latency [207], although, some have been detected during lytic infection as well [139,207–209]. KSHV-encoded miRNAs play a significant role in growth, signaling, and angiogenesis [210–212]. It has been shown that the KSHV-encoded miRNA miR-K12-3 directly activates G Protein-coupled receptor kinase 2 (GRK2) to upregulate the migration and invasion of endothelial cells by activating the CXCR2/AKT signaling axis [140]. Similarly, expression of KSHV-encoded miR-K10a, alone, has been found to be sufficient to transform cells, probably through repressing miR-142-3p targets, which have been shown to inhibit transformation [213]. Downregulation of TGF β signaling plays a significant role in promoting cell proliferation during KSHV infection. KSHV-encoded miR-K12-11 targets SMAD5 to downregulate TGF β signaling, promoting cell survival and progression [141]. In addition, inhibition of miR-K12-11 has been found to de-repress TGF β signaling in KSHV-infected B cells [141]. TGF β signaling has been regulated by thrombospondin 1 (THBS1), a target of the KSHV-encoded miRNAs miR-K12-1, miR-K12-3, miR-K12-6, and miR-K12-11 [142]. THBS1 is an anti-angiogenic factor, and its downregulation leads to repression of TGF β signaling [205]. Furthermore, miR-K12-6 and miR-K12-11 target the cellular transcription factor MAF to reprogram the blood vessel endothelial cells (BECs) and LECs [143]. Downregulation of MAF by the miRNAs increases the expression of BEC marker genes in the KS tissues. KSHV-encoded miRNAs also repress the expression of breakpoint cluster region protein to enhance Rac1 activity and promote in vitro angiogenesis [214]. Thus, KSHV-encoded miRNAs are capable of altering growth signaling pathways and increasing angiogenesis in support of KSHV-associated tumors [214,215].

Kaposin B: The KSHV protein Kaposin B, translated from the DR repeats and K12 interacts with MK2 kinase via the DR2-encoded sequences, thereby enhancing its activity [151]. Kaposin B interacts with the “C-lobe” region of MK2, a region also targeted by p38 kinase [151]. MK2 activation leads to stabilizing high-turnover cytokine mRNA, including pro-inflammatory and angiogenic IL-6 [151]. In addition, Kaposin B stabilizes the PROX1 mRNA, the “master regulator” of lymphatic endothelial cell differentiation [152]. Stabilizing PROX1 mRNA defines a mechanism by which KSHV infection reprograms the blood-to-lymphatic endothelial marker transition, which is believed to be a critical process in KS development [152,216,217].

K15: K15, another KSHV ORF consists of eight exons located at the right end of the KSHV genome, between ORF75 and the terminal repeat (TR) region. K15 is predominantly expressed during the lytic cycle, but some K15 transcripts have been detected in resting PEL cultures [218–220]. Cellular signaling pathways activated by K15 include the Ras/MAPK, JNK/SAPK, and NF- κ B pathways and the

NFAT/AP1 transcription factors [221–223], and induce an angiogenic and pro-inflammatory response. This signaling induces the transcription of a number of cellular cytokines and chemokines, including IL-6, IL-8, CCL20, CCL2, CXCL3, IL-1a/b, and COX-2 [147,224]. Depletion of K15 from the KSHV genome severely affects virus-induced angiogenesis in primary endothelial cells [144]. Kaposi's sarcoma-associated K15 protein, via its SH2-binding motif, also regulates expression of miR-21 and miR-31 to promote cell migration and invasion [145,220]. Furthermore, in KSHV-infected primary endothelial cells, K15 binds to PLC γ 1 and activates calcineurin and NFAT1 to upregulate the expression of host factor RCAN1/DSCR1, inducing angiogenesis and endothelial tubule formation in Matrigel-based assays [144]. Thus, the pro-survival and paracrine-mediated, pro-angiogenic roles of K15 may contribute to KSHV-induced tumorigenesis.

K1: K1, a variable ITAM-containing protein (VIP) is a transmembrane glycoprotein, encoded by the first ORF of KSHV. K1 increases the angiogenic characteristics in cultured primary endothelial cells [68,153] and induces angiogenesis by upregulating VEGF production in primary human endothelial cells [153,225–227]. K1 signaling can activate secretion of inflammatory cytokines, including IL-6, GM-CSF, IL-1b, IL-8, and IL-10, which are directly implicated in development of KS lesions [225,228]. K1 binds to the m-chain of B-cell receptors (BCRs) to retain the complex in ER and decrease the surface expression of BCRs, thereby improving the longevity of B-cells [229]. Additionally, K1 activation of AKT results in inhibiting the pro-apoptotic forkhead (FKHR/FOXO) transcription factor family, which protects the cells from FKHR- and Fas-mediated apoptosis [113]. Similarly, miRNA-891a-5p mediates synergistic induction of angiogenesis by HIV-1 Tat and KSHV K1 through NF- κ B signaling [230]. It has been shown that K1 recruits and activates the Src-family kinases PI3K and PLC γ to mediate signal transduction via several pathways, including ligand-independent, constitutive signaling [231,232]. In KS, PEL, and MCD, K1 exerts a paracrine influence on latently infected and uninfected neighboring cells [233,234]. Overall, these studies suggest that K1 is a multifunctional protein that can constitutively activate multiple pro-growth signaling pathways in KSHV-infected cells. In addition, KSHV acts to promote angiogenesis when co-infected with HIV. The KSHV K1 protein has been reported to act synergistically with the HIV-1 regulatory protein, NEF to induce cell proliferation, vascular tube formation and excessive angiogenesis, in a chicken CAM model [235]. The regulation of angiogenic properties is accomplished by activating PI3K/AKT/mTOR signaling and by downregulating phosphatase and tensin homolog (PTEN) [235]. Since PTEN dephosphorylates PIP3 to PIP2 and inhibits AKT signaling (in other words, cell proliferation), KSHV chooses this molecule to promote tumor formation. PTEN suppression is mediated through the combined effect of HIV-1 Nef and KSHV K1 proteins, which induce cellular miR-718, thereby targeting the sequence in the 3' UTR of the PTEN's mRNA, leading to its inhibition [235]. In a nutshell, KSHV endorses cell proliferative pathways through different signaling molecules for its own interest, which adds up to viral angiogenesis (Figure 2).

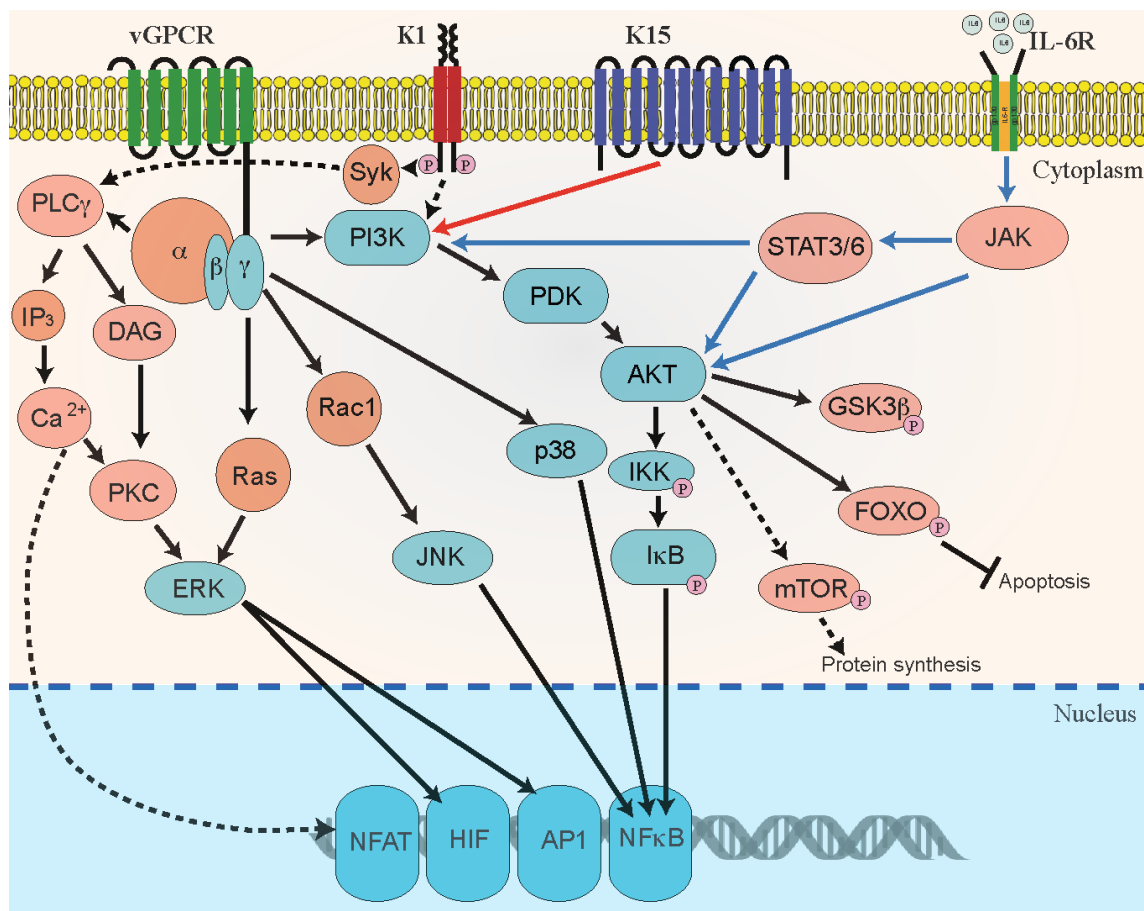


Figure 2. Schematic representation of KSHV-mediated activation of angiogenic signaling pathways. Signaling pathways that are regulated by KSHV proteins viral G protein-coupled receptor (vGPCR), K1, K15, and vIL-6 in B-cells and endothelial cells contribute to KSHV-mediated cellular transformation and angiogenesis through autocrine and paracrine mechanisms. KSHV GPCR and K1 promote cellular signaling through phosphatidylinositol 3-kinase (PI3K), mitogen-activated protein kinases (MAPK) phosphoinositide-dependent kinase (PDK), AKT/protein kinase B (AKT/PKB), and mTOR signaling pathways. Activation of these signaling pathways stimulates the activity of various cellular transcription factors, such as activating protein-1 (AP-1), nuclear factor (NF)-B, hypoxia-inducible factor-1 (HIF1) and Nuclear factor of activated T-cells (NFAT). These transcription factors, in turn, upregulate the secretion of pro-angiogenic growth factors. Signaling through KSHV GPCR is shown as solid black lines and signaling through K1 is shown as black dotted lines. The cellular signaling mediated through K15 and IL-6 receptors are shown as solid red and blue lines, respectively.

K5: KSHV-encoded K5, also called modulator of immune recognition (MIR-2), is a viral E3 ligase that is capable of ubiquitinating MHC-I cytoplasmic tail to trigger the internalization and proteasomal degradation of MHC-I complex [236–238]. Overexpression of K5 in human dermal microvascular endothelial cells (HDMEC) has been shown to downregulate ICAM-1 expression and block T-cell recruitment or capture [157,239,240]. K5 also degrades VE-cadherin and disrupts VE-cadherin/ β -catenin signaling and promotes remodeling of endothelial adherens junctions to initiate angiogenesis [159,241]. K5 protein can activate IFN γ receptor 1, thereby leading to the receptor's degradation. In addition, K5 suppresses IFN γ -mediated activation of the JAK/STAT pathway [242]. K5's ubiquitin ligase activity leads to enhanced aerobic glycolysis, thereby initiating lactate production. This K5 activity is mediated through the endocytosis of cellular growth factor-binding receptor tyrosine kinase, which leads to modulation of AKT and extracellular signal-regulated kinase 1 and 2 (Erk 1/2) phosphorylation [243].

vIL-6: KSHV viral interleukin-6 (vIL-6) encoded by ORF K2 shares 24.8% of its amino-acid sequence identity (49.7% similarity) with its cellular counterpart, human IL-6 (hIL-6) [160,244,245]. Nude mice injected with cells stably expressing vIL-6 reportedly grew highly-vascularized tumors [55]. HIV-1-encoded Nef protein [246] can also synergistically enhance vIL-6-mediated angiogenesis. Furthermore, vIL-6 seems to have a dual anti-apoptotic and proliferative effect, as depletion of vIL-6 through shRNA knockdown has reduced the growth rate in KSHV-infected B-cell lines [223]. Similar to cellular IL-6 (cIL-6), vIL-6 could induce gp130 and several other downstream signaling pathways, including JAK/STAT, MAPK, and PI3K/AKT pathways [161,247]. These pathways modulate multiple transcription factors and response elements (REs), including STAT1/3 and STAT5 IL-6 RE, C/EBP, and c-jun promoter IL-6 RE (JRE-IL-6) [248]. Contrary to its defined autocrine role in PEL pathogenesis, vIL-6 is believed to generate KS and MCD primarily by paracrine signaling. Following the induction of RTA expression, vIL-6 is rapidly produced in de novo KSHV-infected cells and in cells undergoing lytic reactivation [249]. In KS lesions, large populations of KSHV-infected cells maintain a latent phase, however, a very small population of cells remain lytically-active. These cells express lytic proteins, including vIL-6, vGPCR, and K1, and ultimately upregulate the expression of cellular inflammatory and angiogenic cytokines [250], including VEGF [251], IL-6, CXCL8 and bFGF, which play important roles in KS development in a paracrine fashion. These secreted effector molecules determine the survival, proliferation, and angiogenesis of KSHV-mediated oncogenesis [252].

vGPCR: KSHV-encoded G-protein-coupled receptor (vGPCR) [253,254] is a viral homologue of the cellular angiogenic IL-8 receptor [166,255]. It is an early lytic protein that significantly contributes to PEL, MCD, and KS development in a paracrine fashion [256,257]. vGPCR modulates cellular signaling through a variety of pathways, including PLC, PKC, MAPK, PI3K/AKT/mTOR, NF- κ B, AP1, and NFAT networks, thereby regulating the secretion of many angiogenic factors, primarily, VEGF, bFGF, IL-1 β , IL-2, -4, -6, and -8, and TNF α [110,257,258]. In turn, these modulators act in a paracrine fashion and can alter the extracellular microenvironment toward KS tumor progression [54,258]. Endothelial cell-specific expression of vGPCR in Tie2-TVA transgenic mice has led to the formation of multifocal and aberrantly-vascularized tumors with histological similarities to KS [112,258]. These results suggest that vGPCR induces the transformation of cells by modulating the paracrine secretion of pro-inflammatory cytokines and angiogenic growth factors [112,258]. vGPCR has the capability to induce HIF-1 α activity through the MAPK and p38 signaling pathways, leading to the phosphorylation of HIF-1 α [119]. Signaling through vGPCR causes cellular survival and stimulation of pro-angiogenic signaling pathways [13,83,119,254,259]. KSHV manipulates vGPCR for its own survival benefit and tumorigenesis.

vIRF-3: KSHV-encoded viral interferon regulatory factor (vIRF-3) is a cellular interferon regulatory factor homolog that regulates cellular IRFs and inhibits innate responses from the cell [260]. Unlike other vIRFs, vIRF-3 is consistently expressed as a latent protein in latently-infected PEL cells and has been referred to as latency-associated nuclear antigen-2 (LANA2) [168,261,262]. In PEL cells, vIRF-3 plays a significant role in maintaining latency and pathogenesis [170,171]. HIF-1 α , a major regulator of VEGF-A [73,263], is controlled by vIRF-3 by direct interaction, which leads to the stabilization of HIF-1 α and aids its nuclear accumulation [73]. In addition, vIRF-3 encourages VEGF production, which promotes angiogenesis. The induction of VEGF through vIRF-3 could be mediated through HIF-1 α . The involvement of vIRF-3 in promoting endothelial tube formation in HUVEC cells has been attributed to the production of VEGF [73]. Importantly, vIRF-3 has also been found to activate c-Myc-directed transcription and to decrease the expression and stability of the tumor suppressor protein p53 [128,264,265]. The pro-survival roles of vIRF-3 may also be due to the inhibition of PML-mediated repression of survivin [266]. Altogether, vIRF-3 activities are likely to be critical to maintaining latency and defining PEL malignancy [169,267].

vCCLs: KSHV ORF K6, ORF K4, and ORF K4.1 encode for three homologues of cellular chemokines; viral CC-chemokine ligand-1 (vCCL1/vMIP1), ligand-2 (vCCL2/vMIP2), and ligand-3 (vCCL3/vMIP3), respectively [57,172]. KSHV-encoded v-cyclin, a homolog of cellular cyclin D2,

activates cellular CDK6 and promotes G1/S phase transition of the cell cycle. Virus-encoded v-cyclin has been reported to have oncogenic potential, as it induces DNA damage, apoptosis, and autophagy [268]. KSHV-encoded v-cyclin has been shown to interfere with normal T-cell development and to induce lymphoma through v-cyclin-CDK6 complex and Notch activation in vivo [268]. The role of v-cyclin in preventing the cellular senescence and G1 phase arrest induced by HTLV-1 Tax and vFLIP has also been reported [269]. The nature of the viral-chemokine-targeted receptors indicates that they may mediate immune evasion by polarizing Th2 and blocking leukocyte trafficking, as demonstrated for vCCL-2 in in vivo experiments [57,173]. Apart from these immune evasion properties, v-chemokines have also been shown to promote angiogenesis by inducing VEGF [57].

4. Mouse Models for Studying KS-Angiogenesis

Mouse models are considered primary in vivo tools used in biomedical research to identify molecular targets and pathways implicated in neo-angiogenesis and tumor progression. In addition, mouse models help validate the efficacy and safety of anti-angiogenic therapies before they are tested in clinical trials. Tumor-transplanted xenograft mouse models have been immensely valuable in understanding the role of angiogenesis and various angiogenic factors during several stages of tumor development [270]. Although significant progress has been made in characterizing KSHV tumor progression, lack of a good small animal model for KS pathogenesis has hampered deeper understanding of specific mechanisms of KSHV contribution to the oncogenic process. At present, the major problem faced by KSHV in vivo mouse models is that murine cells do not support the complete viral replication and infection program [271].

KSHV-encoded vGPCR, a homologue of the IL-8 receptor, plays an indispensable role in KSHV-mediated angiogenesis and tumor development. As an interesting approach to studying KS tumor development and pathogenesis in mice, Zhang et al. have recently developed a recombinant murine gamma herpesvirus (γ HV68) carrying KSHV vGPCR [272]. Mice infected with this recombinant γ HV68 developed angiogenic, inflammatory features that closely resembled human KS. Mice infected with recombinant γ HV68 carrying vGPCR could potentially serve as an important model for studying angiogenesis and tumorigenesis induced by human gamma herpesvirus in the context of viral infection. Another group has explored the functional role of the KSHV ORFK1 gene on lymphoproliferation and Fas-mediated apoptosis in transgenic mice [273]. Histological evaluation of K1 transgenic mice indicated the development of lymphoid hyperplasia and splenomegaly, as observed in lymphoma, MCD, and angiosarcoma, suggesting that K1 may contribute to the development of KSHV-associated cancers [273].

In addition, several other mouse models have been developed recently (reviewed in [274]) to study KSHV infection and replication. A major advancement in KSHV research was the generation of the humanized-bone marrow, liver, and thymus (hu-BLT) mouse model to test KSHV infection with recombinant KSHV (rKSHV.219) via various natural routes of infection, including the oral mucosa and intra-vaginal routes [271]. These results showed that KSHV could establish robust latent and lytic infections in human B-cells and macrophages. Therefore, humanized mice may become a promising model for studying KS infection in vivo and routes and extents of viral infection in infected hosts [271]. Similarly, another research group has recently developed two new murine models for studying KS infection and pathogenesis. Murine bone marrow-derived endothelial cells were transfected with bacterial artificial chromosome BAC36 (mECK36 cells) to create a stable population of mECK36 cells, which were subsequently injected into immuno-deficient mice [275]. Even though mECK36 sarcomas consisted of latently- and lytically-infected spindle cells, for some reason these mice were not able to produce infectious virions. When the BAC36 in the mECK36 cells were replaced with rKSHV.219 and injected into the mice, they developed tumors that produced herpesvirus-like particles, as observed by electron microscope [275]. In addition, to evaluate the ability of these cells to support lytic replication, they were treated with trichostatin A (TSA), a histone deacetylase (HDAC) inhibitor, to induce viral

reactivation. These models expressed several KSHV lytic genes and productively infected tumors *in vivo*, suggesting that they could be used therapeutically to test targeted antiviral compounds.

5. Current Treatment Strategies for KS Tumors

The growth of functional vessels during angiogenesis requires a synergistic interaction between numerous endothelial growth factors, receptors, and multiple cellular-signaling pathways [276]. A better understanding of this process enables identification of potential targets for inhibiting neovascularization [277]. In the case of KSHV-induced angiogenesis and oncogenesis, targeting either the cellular and viral proteins with a postulated link to angiogenesis or the virus-mediated signaling pathways, may provide a new treatment for KSHV-mediated, aberrant angiogenesis of endothelial cells. Interestingly, a promising new study has shown that Fumagillin, a potent natural angiogenesis inhibitor, induces KSHV lytic/RTA gene expression and KSHV genome replication and inhibits cell growth in stimulated PEL cells [278]. The inhibitory behavior of TNP-470, a synthetic analog of Fumagillin, on angiogenesis has been predicted to be associated with the upregulation of p21 expression in endothelial cells by activating p53 pathways [279]. Current options for tumor therapies include chemotherapy, cytotoxic drugs, combined anti-retroviral therapy, and immune modulators. A general approach to targeting tumor angiogenesis involves using either anti-VEGF monoclonal antibodies or tyrosine kinase inhibitors (TKIs) [277]. Most of the compounds with anti-angiogenic activities that enter the drug-development process have been reported as targeting the VEGF ligand or its receptors/VEGFRs. Several multi-targeted TKIs that block the signaling of pathways, including VEGFs, PDGFs, and c-kits, have been developed and approved for treatment of other malignant tumors [45]. Hence, it is appropriate to use these approved anti-angiogenic drugs to treat KS. Table 2 lists some of the commercially available anti-angiogenic drugs currently used to treat KSHV-mediated cancers.

Table 2. List of commercially available anti-angiogenic drugs for the treatment of KS.

Name of the Drug	Manufacturer	Target	Efficacy	Reference
Imatinib	(Gleevec, Novartis, Basel, Switzerland)	An inhibitor of tyrosine kinases such as Abl, PDGFR and c-kit.	Treatment with imatinib resulted in partial regression of KS tumors in about one-third AIDS-KS patients on combination retroviral therapy	[278]
Sorafenib	(Nexavar, Bayer Healthcare Pharmaceuticals, West Haven, CT, USA)	A small molecule inhibitor of tyrosine-kinases that inhibits VEGFR, PDGFR, FGFR, c-kit, Raf and stem cell factor receptor.	The use of Sorafenib prevented brain metastasis progression and led to unexpected complete remission in a patient with cardiovascular risk and classical KS	[279]
Bevacizumab	(Avastin, Genentech, San Francisco, CA, USA)	Anti-VEGF-A monoclonal antibody that binds to VEGF and neutralizes its action.	The drug induced complete and partial remission of HIV-KS lesions in 3/16 and 2/16 patients respectively, while receiving highly active antiretroviral therapy (HAART)	[280]
Sirolimus	(Rapamune, Pfizer Inc., New York, NY, USA)	Mammalian target of rapamycin (mTOR) inhibitor.	Sirolimus inhibited the progression of dermal KS lesions in kidney-transplant patients being treated with calcineurin inhibitors	[281]

6. Summary

The growth of new blood and lymphatic vessels is important to the progression and metastatic spread of cancer, and this growth occurs through two significant processes: angiogenesis and lymphangiogenesis. Angiogenesis is mediated by several cellular-signaling pathways, with differential expression of pro-inflammatory and pro-angiogenic chemokine factors reflecting the growth and

spread of cancerous cells. The highly vascular nature and extensive neovascularization of KS tumors indicate that KSHV directly induces angiogenesis in KS lesions in a paracrine fashion. KSHV-mediated angiogenesis plays an important role in the control of KS tumorigenesis, and its inhibition with anti-angiogenic drugs/agents is considered a valuable therapeutic approach. For several years, research efforts have focused on investigating various cellular-signaling pathways, particularly growth factor-associated angiogenic signaling, contributing to KS tumor growth, proliferation, and invasion. Although a link between KSHV infection and angiogenesis has been suggested, it is still unclear which factors actually drive angiogenesis during KS progression. A thorough investigation of these mechanisms could lead to targeting specific signaling pathways that are directly involved in regulating KSHV-mediated angiogenesis. This, in turn, may help to revolutionize current therapeutic approaches and aid in designing novel, targeted, anti-angiogenic strategies to treat KS.

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