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3. MOLECULAR BIOLOGY OF KSHV IN RELATION TO AIDS-ASSOCIATED ONCOGENESIS

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INTRODUCTION: KAPOSI'S SARCOMA AND KSHV/HHV-8

In 1872, the famed Hungarian dermatologist Moritz Kaposi characterized an "idiopathic multiple pigmented sarcoma" which is now known as Kaposi's sarcoma (KS).⁴²⁴ For most of its history, KS has been a rare, slowly progressing neoplasm affecting mainly elderly men of Mediterranean and Eastern European descent. KS was not typically fatal, and patients tended to live ten or more years with the condition, and die of other unrelated ailments.²⁰¹ An abrupt increase in the number of cases of KS among previously healthy young homosexual men was first reported in 1981, ushering in a new era of aggressive, rapidly fatal KS.^{40,155,180,210,401} Since approximately 30% of AIDS patients presented with KS as their initial symptom of HIV infection, KS evolved into a defining characteristic of one of the most devastating infectious diseases in history.^{35,177}

The progressive depletion of cell-mediated immunity and subsequent loss of immune function caused by HIV infection predisposes patients to an array of unusual malignancies.^{177,381} AIDS patients do not have higher incidence of the more common tumors of the breast, colon, or lung than the general population; rather they exhibit a greatly increased frequency of cancers induced by oncogenic viruses such as Epstein-Barr virus (EBV), human papilloma virus (HPV), and Kaposi's sarcoma-associated virus (KSHV), also known as human herpesvirus 8 (HHV-8).^{177,381} Impaired immune surveillance promotes a permissive environment for uncontrolled viral replication, the spread of virus to surrounding cells and tissues, and contributes to the multistep process of tumorigenesis.^{99,428} In the case of AIDS-KS, interactions between immunosuppression, HIV, and KSHV are required for malignant progression. Although HIV infection is neither necessary nor sufficient for the development of KS, it is associated with a much higher frequency of KS and alteration of its natural course.⁹⁹ The HIV epidemic in Africa along with the high prevalence of endemic KSHV infection in the general population has led to an alarming number of cases of KS and KSHV-associated diseases on that continent alone.¹¹⁸ With the recent advent of HAART (highly active antiretroviral therapy), the overall incidence of AIDS-associated neoplasms has declined;⁴⁷⁸ however, factors such as lack of access to treatment, noncompliance with treatment regimens, and the development of drug resistance all contribute to an elevated risk for KS in HIV-infected patients.^{46,204,492} and ensure that KS will present a continuing major health problem for years to come.³⁸¹ Understanding of the molecular biology of KSHV alone and in the context of HIV infection is crucial for the development of therapies to treat and prevent the associated pathological processes.

Discovery

In the 1920s, it was observed that KS occurred more frequently in East and Central Africa. The uneven geographical distribution led to the hypothesis that KS might be caused by an infectious agent.^{173,328} In 1990, a landmark epidemiological study from Beral et al. reported that KS was 20,000 times more likely to occur in people with HIV than in the general population.³⁶ KS was more common in those who had acquired HIV sexually than in those who had acquired it via other routes. The incidence of KS was not related to age or race, but showed a definite geographical distribution, with the highest prevalence in the areas that were the initial foci of the AIDS epidemic.³⁶

The accumulation of the epidemiological evidence suggested the involvement of a sexually transmissible agent in the development of KS, which in western countries had spread mainly among homosexual men. Several groups attempted to identify the unknown agent, and in 1994, Yuan Chang and Patrick Moore used representational difference analysis to identify two fragments of a previously unknown herpesvirus in a biopsy sample from an AIDS-KS patient,⁸⁹ instigating a new era in KS research.

Diseases Associated with KSHV

Since its discovery, extensive studies have demonstrated an etiologic role for KSHV in the development of KS.^{79,113,129,302} The involvement of KSHV in the pathogenesis of KS is now widely accepted based on the following criteria: (1) KSHV genomes are detectable in all clinical forms of KS (classic, endemic, iatrogenic, and AIDS related);^{44,89,91,134,253,301,383} (2) KSHV infection is highly associated with subjects at high risk for developing KS such as HIV-infected gay men;^{167,168,229,403} (3) KSHV infection rate in the general population correlates with KS incidence rate in different geographic regions, e.g., high in some African regions, intermediate in Mediterranean and Eastern European regions, and low in North America;¹⁶⁸ (4) KSHV is detected in the endothelial spindle cells, the neoplastic component of KS lesions;^{43,132} and (5) KSHV DNA sequences in peripheral blood and seroconversion to KSHV are detected prior to the development of KS.^{167,168,291,304,325,326,337,355,360} In addition to its association with KS, KSHV has also been implicated as the causative agent of two other AIDS-associated malignancies: primary effusion lymphoma (PEL)^{80,89} and the plasma cell variant of multicentric Castelman's disease (MCD)^{133,415} and may be pathologically involved with other disorders resulting from dysregulation of the immune system.^{129,384}

Kaposi's Sarcoma—Four clinical forms of KS have been described. *Classic KS* is an indolent tumor of elderly men, most often found in Mediterranean, Eastern European, and Near East regions. *Endemic KS* is prevalent in Central Africa, where it is one of the most frequently occurring tumors. *Iatrogenic KS* has been identified in transplant recipients undergoing immunosuppressive therapy. In western nations, KS became a hallmark of the AIDS epidemic.⁷⁷ The occurrence of KS in young male homosexuals/bisexuals was first reported in 1981.^{40,155,180,210,401} *Epidemic AIDS-KS* is the most common neoplastic manifestation of AIDS in the United States and Europe²⁸⁰ and is one of the diagnostic criteria for AIDS.¹ In contrast to the indolent course of classic KS, AIDS-related KS takes a much more aggressive course.³⁶ AIDS-related KS tends to disseminate widely to mucous membranes and the visceral organs.^{1,424} Despite the different clinical manifestations of KS, the histology of lesions from skin, lymph nodes, respiratory tract, and intestines are very similar.¹ KS is a vascular tumor consisting of interweaving bands of spindle cells, irregular slit-like channels embedded with reticular and collagen fibers, and inflammatory infiltrates of mononuclear cells and plasma cells. The neoplastic components of the KS lesion are the so-called spindle cells due to their characteristic abnormal elongated shapes.⁹⁹ The tumor is highly vascular, containing

abnormally dense and irregular blood vessels, which leak red blood cells into the surrounding tissue and give the tumor its dark color.

Cutaneous lesions are divided into patch, plaque, and nodular stages. The patch stage demonstrates a proliferation of irregularly branching blood vessels, which may be grouped around normal-appearing blood vessels. Perivascular infiltrating lymphocytes and multiple plasma cells are typically present. The irregular vessels are small, flat and widely spaced and comprised apparently normal endothelial cells.¹

The plaque stage is characterized by the appearance of spindle cells forming bundles in the vascular spaces. Mitoses and nuclear abnormalities are more prominent in both the spindle cells and the endothelial cells. Extravasation of red blood cells and macrophages is often evident.

As the vascular and spindle cells continue to proliferate, the characteristic nodular phase of classic KS develops. The nodular lesions are composed of well-defined, densely packed aggregates of spindle cells and vascular spaces arranged into bundles. The vascular slits are often distended by red blood cells. Mitotic figures, extravasated red blood cells, hemosiderin, and hemosiderophages are often present.¹

KS lesions are composed of a mixed-cell infiltrate with hyperplastic spindle-shaped cells that resemble cytokine-activated ECs and monocytes/macrophages by their expression of tissue-specific markers (CD34, vascular-endothelial cadherin, endothelial leukocyte adhesion molecule type 1, CD4, CD14, CD68, and PECAM-1).^{207,444,472} Immunohistology, in situ hybridization, and in situ PCR studies have shown that the majority of spindle endothelial cells in advanced KS lesions as well as atypical endothelial cells in early lesions are latently infected by KSHV.^{43,132,336,353,497} Less than 3% of the KSHV-infected cells in KS lesions have been found to express viral proteins characteristic of viral lytic replication.^{101,227,336,420} The low rate of spontaneous lytic replication is postulated to have a role in KS development through an autocrine and paracrine mechanism, as well as ensuring the continued maintenance of KSHV infection.²⁷⁶

Though the classic form of KS is usually localized to the lower extremities, AIDS-KS commonly involves many other parts of the body. The skin of the face, the extremities, torso, and mucous membranes of the oral cavity are often affected. In one study, 45% of patients presented with one or more lesions along the gastrointestinal tract.⁹⁹

Primary Effusion Lymphoma—PEL, also called body cavity-based lymphoma, is a rare lymphoma commonly found in HIV-infected patients.⁷⁹ This type of lymphoma is characterized as a malignant effusion in the peritoneal, pleural, or pericardial space, usually without a tumor mass.^{69,79} The lymphoma cells are usually monoclonal and of B-cell origin, but display only a few markers of B-cell differentiation i.e., CD20, as well as several activation markers such as CD30, CD38, CD71, and epithelial membrane antigen.^{68,161} PEL cells typically express a 420 kDa isoform of CD138/syndecan-1, suggesting they are in a preterminal stage of B-cell differentiation close to that of plasma cells.^{66,162} KSHV is invariably detected in PEL, and is considered to be a diagnostic criterion for this type of lymphoma.^{79,161} KSHV is detected as either monoclonal or oligoclonal episomes in PEL samples.²²² Similar to that seen in KS lesions, the pattern of KSHV gene expression in PEL is mainly latent.^{132,227,336,362} The majority of cells express the viral latent proteins LANA-1 (ORF73), vCyclin (ORF72), vFLIP (ORF71), kaposin (ORFK12), and LANA-2 (ORFK10.5) with a small percentage (2–5%) expressing vIL-6 (ORFK2).^{132,227,336,362} Proteins of the viral lytic cycle are detected in less than 1% of the tumor cells. Though generally considered to be a lytic protein, vIL-6 expression in PEL may be independent of the lytic replication cascade of gene expression.⁹²

Multicentric Castleman's Disease—MCD is a localized lymphoproliferative condition characterized by expanded germinal centers with B-cell proliferation and vascular proliferation. The plasma cell variant of MCD is more commonly seen in AIDS patients and transplant recipients. MCD is frequently but not invariably associated with KSHV infection.^{11,109,133,415} Immunohistochemical analysis of biopsy specimens has shown that 10–50% of B-cells surrounding the follicular centers of MCD are positive for LANA-1.^{131,132,227,336} Of the LANA-1 positive B cells, about 5–25% also express the KSHV proteins vIL-6 and vIRF-1 (ORFK9).^{227,336} In addition, a small proportion of the mantle zone cells of MCD also express viral proteins associated with lytic replication,^{227,336} suggesting that in MCD, KSHV adopts a less restricted pattern of gene expression compared to that seen in either KS or PEL.

Other Possible KSHV-Associated Disorders—Since the isolation of KSHV DNA from KS lesions in 1994, KSHV has been postulated to be involved in several other disease states resulting from immune dysfunction.

Primary pulmonary hypertension is a progressive disorder characterized by elevated mean arterial pressure that may lead to right ventricular failure, and complex, lumen-occluding vascular lesions resulting from dysregulated endothelial cell proliferation. A study published in 2003 reported a possible association between KSHV infection and the nonfamilial form of this disorder, but follow-up studies were not able to confirm this association.^{108,250}

Hemophagocytic syndrome, also called macrophage activation syndrome and hemophagocytic lymphohistiocytosis, is a reactive disorder of the mononuclear phagocytic system that is characterized by benign generalized histiocyte proliferation with profound hemophagocytosis resulting in the destruction of the formed elements of the blood. The acquired form of this syndrome is associated with underlying disease such as immunodeficiency, and can be triggered by infection or medication.¹⁴² KSHV infection may be able to trigger episodes of this syndrome, but it is not the only viral cause.^{3,384}

Limited evidence indicates a possible role for KSHV infection in other diseases, including pemphigus, salivary gland tumors, bullous pemphigoid, nonneoplastic lymphadenopathies, sarcoidosis, Kikuchi's disease, and multiple myeloma.³

Interaction of HIV and KSHV

As KSHV is a necessary but not sufficient etiological factor for KS, only a small proportion of infected people ever develop KS or KSHV-induced lymphomas. Cofactors such as HIV infection and iatrogenic immunosuppression dramatically increase the risk of developing a KSHV-related malignancy in infected individuals. Among KSHV-infected individuals, the risk of KS is much higher in those with HIV-1 infection than among those with other types of immunosuppression, suggesting a direct action of HIV-1 on KSHV replication and the development of tumorigenesis. These two viruses may interact at the molecular level in coinfecting patients, resulting in increased HIV-1 viral load.²⁹³ Studies have demonstrated that coinfection with KSHV can modulate HIV-1 replication.^{73–76} This occurs either through direct interaction between these two viruses or through secondary effects resulting from the release of cellular factors in response to infection. The KSHV ORF50-encoded reactivation and transcriptional activator (RTA) interacts synergistically with HIV-1 Tat protein in the transactivation of HIV-1 LTR, leading to increased cellular susceptibility to HIV infection.⁷⁶ LANA-1 interacts with Tat and activates HIV-1 LTR.²¹¹ Expression of RTA increases the efficiency of HIV infection in different cell types.⁷⁵ This potentially could result in enhanced HIV spread within the infected organism and faster progression of the disease. On the other hand, HIV-1 infection leads to reactivation of latent KSHV genomes, through Tat.²⁹² HIV-1-encoded Vpr proteins increase intracellular KSHV-gene expression.²⁰⁶ Consequently, HIV infection can promote KS progression. In AIDS-KS, HIV and its Tat protein induce

inflammatory cytokines, which can further promote the pathogenesis of KS.^{137,140} In fact, HIV induced oncostatin-M (OSM) and interferon (IFN)- γ to promote KSHV lytic replication.²⁹⁴ It was shown that HIV infection of PEL cells triggered KSHV reactivation²⁹² while KSHV enhanced HIV replication in acutely infected cells and induced reactivation in latently infected cells.⁷³ HIV-1 Tat also enhanced KSHV infectivity, probably by concentrating virions on cell surface.¹⁶

In order to elucidate the basis for the increased frequency, enhanced aggressiveness, and disease progression seen in AIDS-KS, understanding of the molecular biology of KSHV is required. The remainder of this chapter focuses on describing the structure and genetics of the virus, infection systems and animal models used to study the virus, the viral lifecycle, impact on host cellular pathways, potential oncogenic mechanisms, and specific gene functions.

BIOLOGY OF KSHV

Virion Structure and Assembly

Herpesviruses are members of the *Herpesviridae* family. This family comprises three subfamilies, alpha-, beta-, and gammaherpesvirus. KSHV belongs to the γ_2 -herpesvirus group.²⁸⁸ KSHV and other members of the herpesvirus family share a characteristic architecture in which the double-stranded DNA genome is surrounded by an icosahedral protein capsid, a thick tegument layer, and a lipid bilayer envelope.⁴⁸¹ Mature KSHV has at least 24 virion-associated proteins. These include five capsid proteins, eight envelope glycoproteins, six tegument proteins, and five proteins whose locations in the virion have not yet been defined.^{323,499} The 3D structure of KSHV capsids has been investigated by cryo-electron microscopy.⁴⁸¹ The studies show that KSHV has the same $T = 16$ triangulation number and much the same capsid architecture as herpes simplex virus (HSV) and cytomegalovirus despite limited sequence similarity between corresponding capsid proteins.⁴⁸¹ The principal constituents of the capsids are a major capsid protein (ORF25), two triplex proteins (ORF62 and ORF26), and a small capsid protein of ~19 kDa (ORF65).³²³ Viral assembly within infected cells has yet to be studied.

Genome Structure and Organization

KSHV contains a large double-stranded DNA which is a closed circular episome in the nucleus during latency but is linear during lytic replication. Over 90 genes/ORFs are encoded by a 140 kb long unique region (LUR) with 53.5% G+C content, which is flanked by 20–35 kb terminal repeat regions composed of 801 bp terminal repeat units with 84.5% G+C content (Fig. 1). The KSHV genome shares the seven block organization of other herpesviruses with KSHV unique ORFs present between blocks. These unique genes, some of which are homologs to human genes, were designated names with a “K” prefix followed by number.³⁶⁷ Because of the KSHV genome complexity, the exact number of genes in the genome remains unknown. It is possible that new genes have yet to be discovered. Organization of KSHV genome is closely colinear to that of herpesvirus saimiri (HVS) and rhesus macaque rhadinovirus (RRV) genomes. HVS is the prototypical gammaherpesvirus of the *Rhadinovirus* genus.¹⁴⁴ Sequence analysis indicates HVS shares significant homology with KSHV.³⁶⁷ RRV, a simian gamma-2 herpesvirus closely related to KSHV, replicates lytically in cultured rhesus monkey fibroblasts and establishes persistence in B cells. The similarity between the genomes of RRV and KSHV is high, and almost all of the ORFs/genes in KSHV have at least one homolog in RRV.^{10,388}

Genetic Manipulation of KSHV Genome

Study of KSHV infection and functions of individual genes have been hampered by the lack of viral mutants. For KSHV regulatory genes whose functions have been characterized, most have been examined in cell culture after gene cloning; however, their biological functions in

KSHV infection remain largely unclear.^{129,302} The construction of viral mutants is the most straightforward way to examine the functions of individual viral genes, and has been widely used for other herpesviruses. In recent years, the adoption of the bacteria artificial chromosome (BAC) system has accelerated the study of functions of herpesvirus genes because the genome can be easily modified either by transposon or ET cloning in *E. coli* once the genome is cloned as a BAC. Transfection of the cloned viral DNA into permissive mammalian cells leads to the production of infectious virions without the need for further genetic repair and homologous recombination in the transfected cells.

Recently, Zhou et al. successfully cloned the full-length KSHV genome as a BAC in *E. coli*, and reconstituted it in 293 cells.⁴⁹⁸ The sequences of BAC, GFP and hygromycin-resistance cassette were inserted into the loci between ORF18 and ORF19 by homologous recombination without disrupting the expression of these two genes. The recombinant virus could be induced into productive lytic replication producing infectious virions that are capable of infecting 293 and primary human endothelial cells at high efficiency.^{166,498} To elucidate gene function in the context of KSHV infection, the ET cloning system for BAC mutation was developed to generate mutants. The first mutant of BAC36 was achieved by replacing vIRF with a kanamycin-resistance cassette.⁴⁹⁸ Later K8.1, RTA, gB, and MTA mutants of BAC36 were made using the same strategy and their functions have been further addressed.^{194,242,277,485} Transposition is a powerful tool for modifying DNA molecules and a Tn5-based mutagenesis library of BAC36 has been constructed, in which one mutant with Tn5-disrupted LANA-1 has been used to dissect the function of LANA-1.⁴⁸⁷

Host Range and Cell Tropism

As with all human herpesviruses, KSHV may infect a large proportion of the human population and remain in a latent state throughout most of the life of the host. Although a number of cell types are known to harbor the latent virus, the true latent reservoir(s) remain to be defined. Upon reactivation by immunosuppression, such as in HIV infection, the latent virus switches to lytic replication, producing new virus particles that infect and trigger the proliferation of endothelial cells involved in KS. Alternatively, the latent cells might home to the endothelium and proliferate into spindle cells. An early study demonstrated 78 times higher number of KS-like spindle cells detected in the peripheral blood of HIV-1-infected individuals compared to normal controls.⁵⁸ These peripheral blood-derived spindle cells (PBsc) were shown to express a variety of endothelial cell markers, such as Ulex europaeus I lectin, EN4, EN2/3, EN7/44, CD13, CD34, CD36, CD54, ELAM-1, and HLA-DR. Consistent with these early observations, recent studies suggested that KSHV could infect human fetal mesenchymal stem cells (MSCs) and CD34⁺ hematopoietic progenitor cells (HPCs) and the virus may be disseminated following differentiation of infected HPCs into B cell and monocyte lineages.^{338,483} Thus, MSCs and CD34⁺ HPCs may be reservoirs for KSHV infection and provide continuous sources of virally infected cells in vivo. Several studies also suggest that the lymphoid system could be the reservoir of latently infected cells from which KSHV reactivates under conditions of immunosuppression.^{38,327} Similar to EBV, KSHV displays a tropism for B lymphocytes, since viral DNA has been detected in purified CD19⁺ B cells but not in CD8⁺ cells from the peripheral blood of patients with both KS and HIV infection.^{38,252,327}

The origin of KS tumor cells has been a matter of controversy and many mesenchymal cell types have been proposed.^{34,402} The recent finding of several endothelial markers (including CD31, CD34, CD36, and KDR) on KS tumor cells has supported the theory that endothelial cells are the cell of origin of KS.⁴⁷² More support comes from several studies reporting spindle-shape transformation of different types of human endothelial cells following infection with KSHV.^{106,166} However, the lack of Pal-E and eNOS expression has brought into question the endothelial origin of this tumor.⁴⁷³ Recently, several new endothelial markers have been

identified and characterized. The expression of two such proteins, VEGFR3 (VEGF-C receptor, flt-4) and podoplanin (a membrane glycoprotein), have been found to be restricted to lymphatic endothelium.⁴⁷² KS tumor cells express these two markers of lymphatic endothelium as well as the general endothelial marker CD31, strongly suggesting that KS is derived from lymphatic endothelium.^{350,472}

The most common cell type isolated from AIDS-KS has been the spindle-shaped endothelial-like cells that proliferate in response to inflammatory cytokines and have a limited replicating life span.^{281,329,372,373} The spindle cells isolated from KS lesions of HIV-1-infected individuals are generally hyperplastic nontransformed cells that proliferate in culture with inflammatory cytokines. These cells initially contain KSHV that is rapidly lost as the cells are passaged in culture. Cell lines composed of transformed cells have also been isolated from advanced KS lesions. KS cell lines have been isolated from KS lesions (KS SLK and KS IMM) from two HIV-1 noninfected renal transplant recipients.^{9,251} These cell lines, unlike AIDS-KS spindle cells, are transformed cells that grow in the absence of inflammatory cytokines, contain cytogenetic abnormalities, and induce durable tumor lesions when inoculated into nude mice.^{223,373} Similar to the hyperplastic KS spindle cells, the KS transformed cells have also lost the KSHV genomes. Taken together, these findings indicate that early stage KS is a hyperplasia resulting from proliferation of spindle-shaped endothelial-like cells in response to KSHV-induced angiogenesis and inflammation. However, the spindle-shaped cells, most of which have latent KSHV, may eventually become transformed malignant tumor cells during advanced KS. In support of this concept, it has been experimentally demonstrated that primary human endothelial cells and keratinocytes could be immortalized upon *de novo* KSHV infection.^{78,147} Ectopic expression of a number of KSHV genes also leads to immortalization and/or transformation of various cells, further supporting that KSHV is an oncogenic virus.^{22,165,311,429}

In cell culture, KSHV is capable of infecting a diverse range of human and animal cell types/lines including primary CD19⁺ B cells, HPV-transformed human brain endothelial cells BB18 and 181GB1-4, primary neonatal capillary endothelial cells, human embryonic kidney 293 cells, Ln-Cap cells, human lung carcinoma A549 cells, CHELI (Chediak-Higashi syndrome) cells, squamous cell carcinoma SCC15 cells, human fibroblast cells, human bladder carcinoma T24 cells, human prostate carcinoma DU145 cells, human cervical carcinoma HeLa cells, baby hamster kidney BHK-21 cells, owl monkey kidney OMK637 cells, green monkey fibroblasts (Vero) cells, green monkey kidney CV-1 cells, SLK cells (KS-spindle cells), and murine fibroblast 3T3 cells.^{31,357}

KSHV Infection Systems

Because of the direct involvement of endothelial cells in KS tumors, many groups have focused on infection of endothelial cells and several reports have documented KSHV infection of human primary endothelial cells.^{106,147,166,246,306} In the initial report, KSHV infected only a small number of cells in primary human bone marrow microvascular endothelial cell cultures and primary human umbilical vein endothelial cell (HUVEC) cultures. The KSHV-infected cells acquired a spindle-shape morphology and were maintained for >12 months while the control cultures underwent senescence within 3 weeks of culture.¹⁴⁷ It has been proposed that the small number of infected cells provide a paracrine effect to sustain the cultures. Subsequent study showed that KSHV could infect primary human dermal microvascular endothelial cell (DMVEC) cultures and form colonies or plaques of spindle-shaped cells.¹⁰⁶ Again, the primary-infection efficiency in this system was low, even though the virus eventually infected the entire culture after 2–3 weeks. Paradoxically, to sustain long-term KSHV infection, it was necessary to periodically replenish the cultures with uninfected endothelial cells at a ratio of ten portions of normal cells to one portion of infected cells. To facilitate the manipulation of

primary endothelial cells, HPV E6, E7-immortalized DMVEC cultures were used as targets for KSHV infection.³⁰⁶ In this system, the primary-infection efficiency remained low even though the virus also eventually spread to the entire culture, which could now be stably maintained. In contrast, KSHV infection of telomerase-immortalized microvascular endothelial cells was extremely efficient, reaching the entire culture within 2–3 days of infection; however, the infected cells were unable to sustain persistent KSHV infection, and the cultures quickly lost the virus after several passages.²⁴⁶ The limitations, such as low primary-infection efficiency and/or failure of long-term sustainability for virus growth, of the above-mentioned systems have restricted their use for KSHV characterization, especially virus–cell interactions at the initial stage of infection. Furthermore, even in systems that can sustain persistent KSHV infection, the cultures are predominantly in the viral latent phase.¹⁰⁶ Active viral lytic replication was not observed in any stages of infection in these systems. In contrast to the above systems, efficient infection of HUVEC cultures by recombinant KSHV BAC36 is permissive for lytic replication at the early stage of infection, producing large amounts of infectious virion.¹⁶⁶ Infected cultures form bundles of spindle-shaped cells, which are reminiscent of KS vascular structures, and establish latency at a late stage of infection. The latently infected cells can be induced into lytic replication. Thus, this system can be used for examining KSHV latent and lytic replication, as well as productive primary infection.¹⁶⁶

Animal Models

Animal models have been developed to investigate the *in vivo* behavior of KSHV-related malignancies. In a number of studies, tumors were induced by injecting KSHV-infected PEL cells into mice.^{42,343} In a report, BCBL-1 cells were injected alone or with human peripheral blood mononuclear cells (PBMC) into SCID mice.³⁴³ The lymphomas, which developed at or near the site of injection, appeared to derive exclusively from the injected BCBL-1 cells and not from the injected human PBMC. The tumors induced a marked murine angiogenic response, but known angiogenic cytokines were not detected in the BCBL-1 cells.³⁴³ In a similar more comprehensive study, Boshoff et al. found that injection of either singly (KSHV⁺) or dually (KSHV⁺/EBV⁺) infected PEL cell lines into Nod/SCID mice resulted in a significant pathogenic difference.⁴² PEL-like effusions were observed in the mice following intraperitoneal (i.p.) injection of both types of PEL cells, whereas only the dually infected, but not singly infected, PEL produced an effusion following intravenous injection. Singly infected PELs express an array of cell surface homing receptors very different from most lymphomas, with the potential for both positive and negative effects on effusion formation. Dually infected PEL cells expressed adhesion molecules that were very similar to EBV-positive Burkitt's lymphoma (BL) cells. These differences might explain the differential metastasis to solid tumors (as in BLs) between the PEL types.⁴² Another study hypothesized that PEL cells secrete VEGF to promote the vascular permeability of peritoneal vessels, leading to effusion rather than to neovascularization of tumors. The ability of various lymphoma lines (including both PELs and BLs) to form effusions following i.p. inoculation correlated directly with their respective magnitudes of VEGF release. Coinjection of antibodies specific for VEGF, but not control antibodies, blocked effusion formation by the PELs.¹⁷ A *de novo* infection model of SCID/hu mice by KSHV demonstrated that the virus remained confined to the grafted CD19⁺ B cells, and did not spread to mouse tissue based on the detection of the viral DNA and mRNA.¹²⁶ In a similar model, six of eight mice developed KS-like lesions with angiogenesis.¹⁵¹ Similar to human infection, keratinocytes in the epidermis and spindle cells in the dermis supported a largely latent infection, with rare cells expressing lytic genes. The lack of universal infection suggests that the skin model may allow an analysis of viral and host determinants of permissiveness.¹²⁶ A study published in 2004 describes the attempt to develop a primate model by infecting rhesus macaque with KSHV, either with or without SIV, the simian form of HIV.³⁵⁸ Unfortunately, only a very low amount of viral DNA was detectable, and after 27 months postinoculation, KSHV infection did not result in any observable pathology in either SIV-

negative or SIV-positive animals. Two macaque homologs of KSHV, retroperitoneal fibromatosis-associated herpesviruses (RFHV), were identified in retroperitoneal fibromatosis, a malignancy closely resembling KS.³⁶⁶ Unfortunately, attempts to grow these viruses have not been successful so far. The recently identified RRV is closely related to KSHV, 10³⁸⁸ and when coinfecting with SIV, rhesus macaques develop a B-cell hyperplasia similar to MCD occurring in humans with HIV/KSHV.⁴⁷⁷

THE LIFECYCLE OF KSHV

Like all other herpesviruses, KSHV exhibits two distinct phases of infection. Lytic or productive infection results in the replication of viral DNA, the production of infectious virions, and the death of the host cell. During latent infection, the viral genome is maintained as a circular episome within the host cell nucleus and only a fraction of the viral genes are expressed. The viral episome replicates each time the host cell divides, using existing cellular replication machinery. Although infectious virions are not produced during latency, the viral genome retains the ability to be reactivated into lytic replication.¹²⁹ The molecular mechanisms involved in latency and lytic reactivation are described in details in the following sections.

Mechanisms of KSHV Latency

Expression of KSHV Latent Genes/Transcripts—Latent infection by KSHV involves the expression of only a few of the 90 KSHV genes. Specifically, all KSHV latently infected cells express vFLIP, vCyclin, and LANA-1.^{132,217,377} Interestingly, vFLIP, vCyclin, and LANA-1 are located adjacent to one another in the KSHV genome.³⁶⁷ They belong to a multicistronic transcriptional unit, known as the latency transcript (LT) cluster.¹²⁵ The LT cluster is transcribed from a constitutively active promoter (LTc) which is initiated at nucleotide 127,886, giving rise to a unspliced 5.8-kb mRNA and an alternative splicing a 5.4-kb mRNA, both containing vFLIP, vCyclin, and LANA-1, and a 1.7-kb transcript containing vFLIP and vCyclin (Fig. 1). It is likely that LANA-1 is the principal translation product of the longer mRNAs, whereas both vCyclin and vFLIP are synthesized from the shorter transcript, the latter by way of an internal ribosome entry site upstream of vFLIP.^{37,272} These three genes are separated from the K12 gene, which is expressed at low levels during latency, by an ~4.5 kb KSHV sequence that lacks any significant ORFs, representing the largest coding gap within the unique region of the KSHV genome.³⁶⁷ Surprisingly, 10 of the 12 KSHV microRNAs (miRNAs) identified so far are located within this coding gap, whereas the miR-K10 is found within K12,^{63,342,374} and the miR-K12 is located within the 3'-UTR, 265 nt away from the end of the transcript.¹⁸⁶ All 12 KSHV miRNAs are oriented in the same genomic direction.

MicroRNAs are endogenous approximately 22 nucleotide RNAs that play important gene regulatory roles by pairing to the messages of protein coding genes to specify mRNA cleavage or by repressing productive translation.²⁹ miRNAs' functions ranging from control of cell proliferation, cell death and metabolism, to cancer. Recent discovery of virus-encoded miRNAs indicates that viruses also use this fundamental mode of gene regulation.³¹⁶ The first reported virus-encoded miRNAs were the five viral miRNAs expressed in EBV-infected cells. Among the various families of viruses, the herpesvirus family stands out in establishing long-standing latent infection as a major part in the viral life cycle. It is possible that miRNAs may play a critical role in the establishment and/or maintenance of latent infection initiated by herpesviruses. In fact, the KSHV microRNAs are all expressed in latently infected cells and largely unaffected after induction of lytic replication.^{63,342,374} Computationally predicted targets for KSHV miRNAs include viral genes such as ORF23, 27, 31, 52, 49, 61, 68, K7, K13, and K14, and several B-cell-specific genes involved in apoptosis and signaling.⁶² Recently, another latent promoter was characterized which is embedded within the ORF71-73 transcription unit specifying transcripts that encode ORF71/72 or K12 (Fig. 2). This promoter is initiated at 123,751 and polyadenylated at 122,070 or 117,436.^{62,340} Multiple novel

transcripts initiated from LTc and terminated at either 122,070 or 117,436 have also been identified. These transcripts may also be the source of miRNAs.³⁴⁰ It is believed that the transcripts initiating at the two latent promoters present in the KSHV latency-associated region can undergo two entirely distinct fates, i.e., processing to give a kaposin mRNA and viral microRNAs on the one hand or expression as KSHV vFLIP, vCyclin, or LANA-1 mRNAs on the other, depending on whether the viral polyadenylation site located at position 122,070 is ignored or recognized, respectively.⁶²

The KSHV K15 is another gene that has been detected in latently infected cells; however, the expression levels of this transcript increase following induction of lytic replication.¹⁰³ The K15 gene is encoded by the last ORF in the KSHV genome, adjacent to the terminal repeats, and is transcribed in a leftward orientation away from the terminal repeat region.¹⁰³ The K15 gene contains eight exons which undergo alternative splicing, yielding several isoforms with a predicted common carboxyl-terminal cytoplasmic tail and different numbers of transmembrane domains.¹⁰³

ORFK10.5 encodes latency-associated nuclear antigen 2 (LANA-2/vIRF-3), which is expressed in KSHV-infected hematopoietic tissues, including PEL and MCD but not KS lesions. LANA-2 is abundantly expressed in the nuclei of cultured KSHV-infected PEL cells. Transcription of K10.5 in PEL cell cultures is neither inhibited by DNA polymerase inhibitors nor significantly induced by phorbol ester treatment.³⁶²

Mechanism of KSHV Episomal Persistence—LANA-1, originally named latent nuclear antigen (LNA), is the dominant protein expressed during latency.¹⁶⁷ LANA-1 is a multifunctional multidomain protein of 1,162 amino acids in length, 222–234 kDa in size, with a characteristic speckled or punctate nuclear localization.^{167,168,229} LANA-1 has three domains: (1) a 329 aa N-terminal rich in serine/threonine, proline, and basic residues; (2) a highly polymorphic 534 aa internal repeat domain (IRD) rich in glutamic acid, aspartic acid, glutamine, and leucine and contains a putative leucine zipper motif; and (3) a 227 aa C-terminal domain rich in charged and hydrophobic residues.^{169,495} Because the KSHV viral genome does not encode any of its own centromeres, it must have an alternative method for maintaining and replicating its episome from generation to generation. In KSHV, LANA-1 is responsible for episomal maintenance, replication, and segregation into daughter cells.

In order to carry out these functions, LANA-1 tethers the KSHV episome to the chromosome.^{25,27,112,285,398,433} In KSHV-infected cells, LANA-1 colocalizes with KSHV and binds episomes.^{25,238,441} Because of this colocalization, LANA-1 was implicated as an important element in episomal persistence and there is much *in vitro* evidence to support this conclusion. LANA-1 expression is sufficient for maintenance, replication, and segregation of plasmids containing terminal repeat units.^{170,184,205} LANA-1 is sufficient and necessary for viral latent DNA replication and efficient episomal segregation during mitosis, which assures that an equal number of KSHV episomes is distributed to each daughter cell.^{25,184,205} Transposon-mediated disruption of LANA-1 protein expression in recombinant KSHV BAC36 renders the virus incapable of establishing latency and leads to the loss of the episome, demonstrating that LANA-1 is essential for these functions *in vivo*.⁴⁸⁷

LANA-1 utilizes protein–protein interactions with the folding regions of core histones H2A and H2B to facilitate episomal tethering to the nucleosome during mitosis and interphase.²⁷ Both the N- and C-terminal domains of LANA-1 interact with the host chromosomes; however, the C-terminal cannot maintain the KSHV episome in N-terminal mutants.^{26,27,243,345,398} It is most likely that LANA-1 binds to two unique sites in the long terminal repeat of the KSHV episome with its C-terminal and the chromosomes with the N-terminal while the C-terminal plays a supportive role in binding KSHV episomes to host chromosomes. Nevertheless, the C-

terminal is important for LANA-1 oligomerization and evidence suggests that oligomerization is important for efficient tethering of the KSHV episome.^{385,447,452} The LANA-1 C-terminus also interacts with a number of chromosome binding and origin recognition complex (ORCs) proteins such as Brd2/RING3, CBP, ORC2, and HBO1 to create an optimal microenvironment for episomal replication.^{423,447} When the expression levels of these proteins are knocked down by siRNAs, the efficiency of episomal replication is also reduced, indicating that the C-terminal is likely essential for ensuring episomal replication.⁴²³ Thus, in addition to tethering the episome to the chromosomes, LANA-1 ably hijacks cellular proteins to aid the virus in episomal replication.

Mechanisms of KSHV Reactivation

Expression of KSHV Lytic Genes—A hallmark of herpesvirus life cycle is the expression cascade of genes that can be divided into four categories based on their expression kinetics: latent, immediateearly (IE), early, and late genes. The IE genes are expressed immediately after primary infection or upon reactivation from latency, and do not require de novo protein synthesis. IE genes generally encode for regulatory proteins and are critical for initiating viral transcription. RTA is the gene product of the major IE transcript of KSHV, which is necessary and sufficient to drive the switch from latency to lytic gene expression and the production of viral progeny in infected cells. KSHV may also encode several other IE gene products, including ORF45, ORF29b, and ORF4.2.²⁴⁵ ORF45 is present in purified KSHV virions and appears to be a tegument protein.^{499,502} ORF45 was characterized as a phosphorylated protein and may interact with IFN regulatory factor 7 (IRF-7) and inhibit virus-mediated induction of IFN- α/β .⁵⁰¹

Early gene products are made after the IE genes, but prior to viral DNA synthesis; therefore, their expression is not affected after the inhibition of viral DNA replication by agents such as phosphonoacetic acid (PAA). Several KSHV early genes have also been identified; they include K8 (K-bZIP, also known as RAP), vIRF-1, K1, K3, and K5 (MIR-1 and MIR-2, modulator of immune recognition proteins 1 and 2), ORF57 (a functional homologue of the EBV MTA gene), vIL-6, viral CC chemokine ligands (vCCLs), polyadenylated nuclear (PAN) RNA, vBcl-2, ORF49, K12, K15, viral G protein-coupled receptor (vGPCR), viral dihydrofolate reductase (vDHFR), and thymidylate synthase.^{47,48,96,178,195,257,300, 340,361, 377,431,439,466,467,476}

Late genes whose expression is abolished by PAA usually do not appear until 30 h after induction.^{431,500} Examples of these proteins include envelope glycoproteins gB, K8.1, and a small viral capsid antigen encoded by ORF65.^{181,377,431}

Molecular Mechanisms Involved in KSHV Reactivation—The switch from latent to lytic infection of KSHV is initiated by a number of stimuli that induce the expression of the key lytic switch protein, RTA. The expression of RTA is necessary and sufficient to trigger the full lytic program resulting in the ordered expression of viral proteins, release of viral progeny, and host cell death.^{275,276,430} The expression of RTA precedes the expression of all other cycloheximide-resistant IE genes and cycloheximide-sensitive early genes. In addition, activation of RTA leads to the complete replication of nascent, infectious virus particles with kinetics that is consistent with stimulation by chemical inducers.¹⁸¹

Following primary infection, KSHV generally establishes latent infection.³¹ During latency, only a few genes are transcribed, while the expression of RTA is tightly repressed. However, cloned promoter region of RTA shows a high basal activity,^{95,121,370} indicating that epigenetic change and chromatin remodeling of KSHV genome may be involved in this repression. Epigenetic changes such as DNA methylation act to regulate gene expression in normal mammalian development as well as in cancer through transcriptional silencing of critical

growth regulators.³⁰ With approximately 70% of the CpG sites in the human genome methylated, it is clear that the cellular environment is predisposed toward methylation, and a herpesvirus infecting a host cell must contend with this environment. In fact, before the discovery of KSHV in 1994⁸⁵ the genomes of the known gammaherpesviruses (including EBV and various murine, bovine and simian family members) were all shown to be CpG suppressed, suggesting they too have been subjected to heavy methylation.²²⁶ The finding by Chen et al. 95 suggested a mechanism that hypermethylation in the RTA promoter may regulate its expression and subsequently KSHV reactivation from latency. Other chromatin modifications, such as histone deacetylation and alterations of chromatin-binding proteins, affect local chromatin structure and, in concert with DNA methylation, may also regulate RTA gene transcription.²⁷³ It has been suggested that methylation of the RTA promoter region during latency promotes the association of transcriptional repressors and histone deacetylase (HDAC). Lytic replication of KSHV can be triggered by chemical agents including butyrate and 12-*O*-tetradecanoylphorbol-13-acetate (TPA). Butyrate, a known activator of lytic replication, is an inhibitor of HDAC, and conversely, TPA is an inducer of histone acetylases (HAT). Therefore, both inducers of KSHV lytic replication are affecting the acetylation state of the RTA promoter that is in turn dependent on methylation. Such findings imply that the control of latency and of lytic switching is a function of chromosomal architecture, and will involve the interplay between viral RTA and host factors that regulate chromatin methylation and acetylation.⁴⁷⁴

RTA can also autoactivate its own expression.^{121,370,387} A striking feature of RTA-mediated lytic gene expression was that RTA induced KSHV gene expression in a more powerful and efficient manner than TPA stimulation, indicating that RTA plays a central, leading role in KSHV lytic gene expression.³¹⁸

After activation, RTA is recruited to its responsive elements through direct interaction and transactivation with RBP-Jk, a notch signal pathway transcription factor, to activate viral lytic gene expression.^{83,84,199,262,263,474} Interestingly, RTA also contributes to the establishment of KSHV latency by activating LANA-1 expression through the notch signaling pathway RBP-Jk. On the other hand, LANA-1 can inhibit viral lytic replication by inhibiting expression as well as antagonizing the function of RTA.²⁴⁸ The interaction between RTA and LANA-1 provides a feedback mechanism by which these two proteins can regulate each other and is likely to be a key event in the establishment of KSHV latency.^{247,249} RTA may also recruit CBP, the SWI/SNF chromatin remodeling complex, and the TRAP/mediator coactivator to its down-stream viral promoters, and that this recruitment is essential for RTA-dependent viral gene expression.¹⁹⁰

RTA mRNAs and Protein Structure—Multiple transcripts were found to be encoded by the ORF50 region; the main transcript is a 3.6 kb mRNA that encodes the entire RTA. In addition, a downstream gene, K8 was also found to be encoded within the same RNA species. RTA protein is mainly encoded by ORF50 but obtains an additional 60 amino acids for its N-terminal through a splicing event which shifts its start code across ORF49.^{96,430} The transcript for RTA can potentially encode for a protein of 691 amino acids, and is predicted to have a molecular mass of 73.7 kDa. However, the expressed protein when analyzed by Western-blotting appears to be about 110 kDa, suggesting that RTA could be modified post-translationally by phosphorylation or by other mechanisms.²⁷⁵ RTA lacks any significant homology with cellular proteins but is functionally and genetically homologous the RTA proteins from EBV, HVS, RRV, and MHV68.^{116,179,268,482} The RTA protein consists of an N-terminal DNA binding domain, a central dimerization domain, a C-terminal acidic activation domain, and two nuclear localization signals (NLS).⁹⁶⁻²⁷⁵ The DNA-binding domain of RTA is located at the amino terminus from aa 1 to 530. A deletion mutant of the activation domain sequences (aa 531–691), containing only the DNA binding domain, has been shown to be a trans-dominant-negative mutant that maintains DNA-binding activity for RTA responsive

promoters but no longer activates lytic gene expression.²⁷⁵ The activation domain is located at the carboxyl terminus of the protein (aa 486–691) which is highly acidic and contains numerous charged amino acids.²⁷⁵ This region also contains four repeated units of a highly hydrophobic domain with sequence homology to other transcriptional factors such as VP16 domain A.²⁷⁵ These characteristics suggest that KSHV RTA is a member of a family of transcriptional factors.⁴⁷⁴

Downstream Targets of RTA—RTA has been shown to regulate and transactivate a number of downstream viral genes that function in lytic replication, including K1, K3, K5, DNA polymerase, vIL-6, vIRFs, vGPCR, K12, K15, etc.^{47,48,120,121,178,195,275,370,414,445,476} RTA activates downstream KSHV target genes by at least two mechanisms: direct recognition of RTA response elements (RRE) in the promoters of its target genes and interaction with cellular or viral proteins bound to the promoters.^{83,413} For example, RTA directly binds to the promoters of PAN and K12 but does not bind to ORF57 or vCCL-1 promoters. Conversely, RTA transactivates the promoters of ORF57 and vCCL-1 through the binding of a cellular factor, RBP-Jκ protein.⁸⁸

There is no defined consensus sequence for direct RTA binding and there is no significant homology present in the RTA-responsive viral promoters. However, a comparison of the K8 RRE with other viral RRE revealed a pattern of multiple A/T triplets spaced with a periodicity of 10 or 20 bp.²⁶⁴ The diversity of RTA binding pattern implies that the activation of RTA target gene promoters may result from RTA interaction with other cellular or viral proteins that mediate the DNA-transcriptional complex interaction. One such cellular factor could be NF-κB.³⁶³ Other cellular factors involved in RTA transactivation may include TATA-binding protein such as the case in the K1 promoter.⁴⁸ RTA may regulate vOX-2 (K14) and vGPCR genes through an IFN-stimulated response element (ISRE)-like sequence (K14 ISRE) in the promoter region.⁴⁹³

Cellular Factors Involved in RTA-Mediated KSHV Reactivation—Identification of cellular proteins that coordinate with RTA in transactivation and characterization of the mechanisms whereby such host–viral protein complexes mediate the switch from KSHV latency to lytic replication is an important step in understanding the virus life cycle and pathogenesis. Increased viral lytic reactivation has been observed following exposure of latently infected PEL cells to agents such as IL-6, IFN-γ, hypoxia, other viral agents, *n*-butyrate, ionomycin, 5-azacytidine, and TPA.^{86,92,95,117,123,198,292,295,303,359,412,451,504} Cellular pathways involved in the induction of viral lytic reactivation include the NF-κB pathway, and the protein kinase C (PKC) δ, and MEK/ERK, JNK, and p38 MAPK pathways.^{107,123,333,392} AP-1, the cellular activator protein complex composed of c-Jun and c-Fos heterodimers, mediates the transcription of MAPK target genes.⁴⁶³ The RTA promoter contains a consensus AP-1 binding site,⁴⁶³ and the OriLyts (origins of lytic replication) also contain several putative AP-1 binding sites.¹⁹ The presence of AP-1 binding sites in these regions allows the virus to respond to cellular conditions that may not be favorable for latency. NF-κB has been shown to be constitutively active in PEL cells²³¹ and promotes their survival. The involvement of NF-κB in lytic reactivation is controversial.^{56,392} One study reported that inhibition of NF-κB led to increased viral lytic protein synthesis in KSHV-infected epithelial cells and PEL cells,⁵⁶ however, another study demonstrated a requirement for NF-κB activation for the production of infectious virions.³⁹² In the latter study, virion production was not diminished by suppression of NF-κB, but infectivity of the virions was decreased, suggesting NF-κB may be involved in multiple aspects of lytic reactivation and viral production. In addition, cellular pathways contributing to epigenetic effects such as DNA methylation and histone acetylation may also participate in the reactivation of KSHV.^{95,273}

The direct interaction of (CREB)-binding protein (CBP) and p300 with KSHV RTA in the activation of lytic replication has recently been reported by Hwang et al.¹⁹¹ HDAC was shown to repress RTA activity by binding directly to the proline-rich sequences in the RTA central domain aa 301–449. Specific inhibition of HDAC by trichostatin A (TSA) derepressed the inhibition of RTA and stimulated RTA-directed gene expression. KSHV RTA strongly induces CD21 and CD23a expression through RBP-J κ binding sites and regulates RBP-J κ -mediated cellular gene expression, which ultimately provides a favorable milieu for viral reproduction in the infected host.⁸⁴ RTA was also shown to interact with other cellular factors such as RAP, C/EBP α , CBP, STATs, RBP-J κ , SWI/SNF, TRAP230, PKC, MAP kinase, AP-1, NF- κ B^{190,191,193,209, 258,265,423,462,464,480,484,488} and transactivates target genes through Oct-1 and Sp-1.^{370,445}

Recently, Wang et al. reported that IRF-7 negatively regulates KSHV lytic reactivation by competing with RTA for binding to the RTA response element in the ORF57 promoter to down regulate RTA-induced gene expression.⁴⁵⁸ Yu et al. reported that IRF-7 is targeted for degradation through an ubiquitination-dependent fashion, and RTA itself acts as a ubiquitin E3 ligase.⁴⁹¹ Previously, Zhu et al. reported that ORF45 blocks the phosphorylation and nuclear translocation of IRF-7 and efficiently inhibits the activation of IFN- α/β genes during viral infection.⁵⁰¹

KSHV Primary Infection

Characterization of KSHV primary infection relies heavily on the development of systems with high infection efficiency. KSHV isolated from PEL and sometimes KS lesions is able to infect various cell types but with limited primary infection efficiency or unsustainable infection culture (see Sect. A). Of all the systems examined so far, KSHV eventually establishes latency after primary infection. In some studies, KSHV was found to immediately enter latency. However, other studies have indicated that KSHV has an early full productive replication phase during infection in at least some cell types or infection conditions.^{124,149,166} In fact, in the first description of KSHV infection and transmission system in 293 cells, cytopathic effect (CPE) was observed after primary infection, an indication of lytic replication.¹⁵² In both MVDEC and HUVEC, KSHV linear genomes and lytic transcripts were detected several days after primary infection, again indicating productive primary infection.¹²⁴ Strikingly, efficient infection of HUVEC by recombinant KSHV BAC36 is lytic replication-permissive at the early stage of infection, producing large amount of infectious virions.¹⁶⁶ Examination of the expression of lytic proteins and transcripts further confirmed KSHV productive lytic replication in this system.^{166,489} BAC36 infection of HUVEC displayed two phases: an early productive phase, in which the virus actively replicates producing large number of virions, and concomitantly resulting in massive cell death; and a latent phase, in which the virus switches into latent infection in the surviving cells.¹⁶⁶ Similar results were also observed in a separate study.¹⁴⁹ The different results from these studies point to the variations of cell types in supporting KSHV productive primary infection. The determination of the cell types and/or conditions that can support KSHV productive primary infection and the delineation of the underlying molecular basis could help understand the mechanism controlling KSHV replication and latency.

Attachment, Entry, and Cellular Receptors—Enveloped viruses infect host cells in two steps. The first step is attachment, or binding, of the virus particle to host cell receptors. This step is mediated by the interaction of viral proteins with cell surface molecules such as glycosaminoglycans (i.e., heparan sulfate).⁴¹⁶ Attachment allows other viral proteins to contact cellular coreceptors, which will then stimulate the second step, entry, by either a fusion event between viral envelope and cell membrane, or receptor-mediated endocytosis.⁴¹⁶

Similar to other herpesviruses, KSHV expresses several transmembrane glycoproteins that are virion associated, and involved in the attachment and entry of target cells. KSHV glycoproteins gB (ORF8), gH (ORF22), gL (ORF47), gM (ORF39), and gN (ORF53) are all conserved among the herpesviruses. In addition, KSHV encodes several unique glycoproteins K1, K8.1A, K8.1B, and vOX-2 that share no significant homology with glycoproteins of other herpesviruses.^{82,105,240,242,261,277}

The ability of KSHV to infect a variety of cell types in vivo and in vitro^{7,31,164,303,357} indicates that it must be able to recognize either ubiquitously expressed cell surface receptors, or more than one type of receptor. To date, KHV has been shown to attach to the cell surface molecules heparan sulfate, integrin $\alpha\beta 1$, and DCSIGN.^{6–8,39,354,454} K8.1A and gB have both been shown to interact with the ubiquitously expressed heparan sulfate.^{6,8,39,454} Heparan sulfate is a linear carbohydrate that is localized at the extracellular cell surface, typically covalently bound to a core proteoglycan imbedded in the cell membrane. Heparan sulfate proteoglycans participate in many biological processes including cell–matrix interactions, activation of chemokines, enzymes, and growth factors,⁴⁴⁰ and is well established to be important for the cell attachment of many other herpesviruses.⁴¹⁶

Although conserved among herpesviruses, only KSHV gB contains an RGD motif, which is the minimal peptide region known to interact with integrins in the cell membrane.^{5,7,455} KSHV gB specifically binds integrin $\alpha\beta 1$ through its unique RGD motif.^{7,494} Integrins are a large family of heterodimeric receptors that contain two transmembrane glycoprotein subunits, α and β . There are 24 α and 9 β subunits identified so far, with more than 24 known combinations of these subunits.^{172,346} Each cell expresses several combinations of $\alpha\beta$ integrins, and each combination has its own binding specificity and signaling properties.^{172,346,380,382} Integrin $\alpha\beta 1$ is a receptor for laminin 5 and fibronectin, and is expressed at high levels in endothelial cells.^{220,479,494}

DC-SIGN (dendritic cell-specific ICAM-3-grabbing nonintegrin) is a type II C-type lectin that is found on myeloid dendritic cells in the dermis, mucosa, lymph nodes, lung, and thymus, and IL-4-stimulated monocyte-derived dendritic cells.^{356,409,443} It is also expressed on lung alveolar macrophages,⁴⁰⁹ placenta,⁴⁰⁸ inflammatory lesions⁴¹¹ and IL-13-stimulated, monocyte derived macrophages,^{94,409–411} DC-SIGN acts as a pathogen recognition receptor in these cells of the immune system, activating macrophages and dendritic cells to ingest and process pathogens for antigen presentation to T cells.^{94,171} KSHV may have evolved the ability to exploit DC-SIGN in order to infect dendritic cells and macrophages, and interfere with their antigen presentation functions.³⁵⁴

Following attachment to the cell, an enveloped virus such as KSHV can gain entry to the cell by either direct fusion of its envelope with the plasma membrane or by endocytosis, followed by fusion with the endosomal membrane. Evidence for both routes of entry has been published, and KSHV may use more than one mechanism, depending upon the cell type and which receptors are expressed.^{5,124,212,341}

Endocytosis provides rapid and convenient transport of virion across the plasma membrane, through the cytoplasm, and delivery of the viral cargo to the perinuclear region. Endocytosis can occur through four major mechanisms: clathrin-coated vesicles, the caveolar pathway, macropinocytosis, and a poorly characterized nonclathrin, noncaveolar dependent form of endocytosis.^{232,289,400} KSHV is able to infect human fibroblasts via endocytosis as demonstrated by the presence of virus particles inside endocytic vesicles within 5 min following attachment.⁵ The presence of transferrin within the vesicles implicates clathrin-mediated endocytosis as the means used by the virus to enter human fibroblasts. However, it

has been demonstrated for other herpesviruses, i.e., HSV-1, that entry via endocytosis results in nonproductive infection with minimal infection.²³⁷

Fusion of the viral envelope at the plasma membrane has been well established for other members of the herpesvirus family.⁴¹⁶ Some studies indicate that KSHV fuses with the plasma membrane to enter target cells in 293 cells and MVDEC.^{124,212,341} Expression of KSHV envelope glycoproteins gB, gH, and gL in mammalian cells induced cell–cell fusion.³⁴¹ Expression of the cellular membrane protein xCT facilitates the fusion of KSHV-negative cells with KSHV-positive cells BCBL-1 that have been stimulated to express viral lytic proteins, specifically glycoproteins at the cell plasma membrane.²²⁵ Transfection of xCT into cell lines that normally are resistant to KSHV infection rendered them permissive to fusion and infection by KSHV. The xCT protein is a transmembrane protein that is upregulated in response to stress induced by the production of reactive oxygen species.^{351,379} Exposure of endothelial cells to ROS may enhance the infectivity of KSHV.⁴⁵⁹ In addition, the HIV protein Tat has been shown to stimulate the expression of xCT,⁵¹ and Tat can also enhance the infectivity of KSHV.¹⁶

Limited evidence demonstrates that KSHV adheres to the general dogma of herpesvirus family members once inside the host cell. In MVDEC, following envelope fusion with either the plasma membrane or the endosomal membrane, the viral tegument proteins and nucleocapsid are released into the cytoplasm.¹²⁴ The nucleocapsid is then degraded, and the tightly packaged linear viral genome decondenses and is delivered to the nucleus. Within 8 h post infection, the viral genome circularizes, which is the typical conformation of the genome during latency. However by 72 h post infection, both circular and linear genomes can be detected, indicating a mixed population of latent and lytic infection.¹²⁴ In fibroblasts, nuclear trafficking appears to be mediated by microtubules and the associated dynein motors.³²¹ These observations remain to be confirmed in endothelial cells.

Regulation of Cellular Signaling Pathways and Expression of Viral and Cellular Genes—The events that lead to successful infection by KSHV, i.e., attachment, entry, nuclear trafficking, and expression of viral genes, cannot occur without careful manipulation of preexisting host cell signaling pathways and machinery, as well as suppression or evasion of host defenses.

The interaction of glycoprotein gB (discussed above) with cellular integrin $\alpha 3 \beta 1$ activates focal adhesion kinase (FAK) and the MEK-ERK1/2 pathway.^{7,393,394} Primary infection of HUVEC cells causes a conversion from the normal flat “cobblestone” cell morphology to a “spindle cell” typical of the cells seen in KS lesions.¹⁶⁶ Spindle-cell conversion occurs as early as 6 h post infection and requires viral modulation of host cytoskeletal apparatus. Glycoprotein gB mediates this extensive cytoskeletal rearrangement by modulating the FAK-Src-PI3-kinase-RhoGTPase pathway.^{320,393} It has also been reported that glycoprotein gB can activate VEGFR-3 on the microvascular endothelium and trigger a migratory and proliferative response in these cells.⁴⁹⁴ Primary KSHV infection also activates and is dependent on the JNK and p38 MAPK pathways in addition to the MEK-ERK1/2 pathway.^{333,484} The activation of the multiple MAPK pathways is instrumental in the activation of the transcription factor AP-1. AP-1 regulates the expression of a variety of cellular genes, including IL-6, and in fact is required for the transcription of KSHV genes. KSHV induction of AP-1 could also contribute to a variety of KSHV-induced malignant phenotypes such as cellular proliferation, angiogenesis, inflammatory cytokine production, and dissemination of tumor cells.⁴⁸⁴ During primary infection, KSHV-encoded host-modulating genes are expressed which could impact the expression of host genes.^{241,489} Analysis of cellular transcripts during primary infection reveals that KSHV is able to significantly upregulate expression of cellular genes that are implicated in cell growth and survival, inflammation and angiogenesis, and immune responses.³²²

Viral Gene Expression During Primary Infection—The expression profiles of KSHV transcripts during KSHV primary infection depend on the infection systems. In the productive HUVEC primary infection system, the expression of latency-associated genes is generally expressed first preceding the cascade of lytic genes and onset of lytic replication. The transcription of lytic genes peaks around 54 h post infection followed the production of infectious virions.^{166,489} While after 54 h post infection, the expression of lytic genes declines, latency-associated transcripts continue to increase, indicating that following the permissive phase of lytic replication, surviving cells express the latency gene cluster, specifically ORF71/ORF72/ORF73, and have the tendency to switch to latency.⁴⁸⁹ Similarly, KSHV-encoded genes with host modulating functions, including mitogenic and cell cycle-regulatory, immune-modulating, and antiapoptotic genes, were expressed before those encoding viral structure and replication genes, and sustained at high levels throughout the infection, suggesting KSHV manipulation of host environment to facilitate infection.⁴⁸⁹ In the default latency infection systems of fibroblasts and MVDEC, the latent genes are also expressed throughout the infection process; however, lytic genes such as RTA are only transiently expressed, which is consistent with the lack of productive viral replication in this system. Nevertheless, the early expression of lytic genes involved in immunomodulation and resistance to apoptosis also suggests KSHV manipulation of host defenses to facilitate infection.²⁴¹

MECHANISMS OF KSHV-INDUCED PATHOGENESIS

Introduction: KSHV Infection Promotes Oncogenesis

Although it remains controversial whether KS is a malignant neoplasm, at least the late stage of KS lesions are true clonal cancers, probably evolved from a constant reactive, inflammatory/angioproliferative process in immune compromised patients.^{77,138,139} Given the association of KSHV with two different human malignancies (KS and PEL), KSHV is considered to be a human oncogenic virus. Distinctive from other oncogenic viruses, KSHV is a complex DNA virus that not only has the ability to promote cellular growth and survival for tumor development but also can provoke deregulated angiogenesis, inflammation, and modulate the patient's immune system in favor of tumor growth. Nevertheless, not all individuals harboring KSHV develop KS. The presence of KSHV DNA in some healthy individuals indicates that KSHV alone may not be sufficient to cause clinical KS. Since KS is most commonly found in immunosuppressed individuals, it has been suggested that immune deficiency is an important factor in the pathogenesis of AIDS-KS and that HIV infection may be an important cofactor in disease progression.^{54,138,139,176}

The majority of spindle-shaped cells in KS lesions are latently infected by KSHV indicating that latent infection plays an essential role in KSHV-induced malignancy and pathogenesis.^{122,141,422} Nevertheless, a small subset of KS cells also undergoes spontaneous viral lytic replication indicating that KSHV lytic replication might also be important for KS development. There is strong correlation between viral load and progression of KS tumor.^{55,115,135,146,347} Several drugs that target herpesvirus replication have been shown to be effective to inhibit KS tumor growth.^{45,221,296,365} A number of viral lytic genes have been linked to KSHV-induced malignancy and pathogenesis.⁷⁷ The production of infectious virions should lead to new infection, which could also produce virus-encoded cytokines and induce cellular cytokines as stated in Sect. C.

Promotion of Cellular Growth and Survival—Although the pathogenesis of KSHV-induced malignancies is still not completely understood, it appears that the virus targets multiple pathways to promote cell proliferation and survival to facilitate tumor development. Several studies have shown that genetic instability is present in KS tumors and PEL.^{72,119,160,163,348} KSHV infection is sufficient to induce chromosome instability,³³⁴ for which LANA-1 and vCyclin might be partially responsible.^{399,450} Like other oncogenic DNA viruses,

KSHV targets both p53 and pRb tumor suppressor pathways. At least five KSHV genes, LANA-1, RTA, K-bZIP, LANA-2, and vIRF-1, interact with and suppress the functions of p53 and pRb.^{154,192,317,352,362,391,397} Loss or dysfunction of tumor suppressor genes will inhibit the host cell's ability to repair damaged DNA, eliminate p53-dependent cell death, and dictate cell cycle for uncontrolled cell proliferation, hence contributing to KSHV-induced oncogenesis. Furthermore, KSHV can regulate cell cycle progression through vCyclin.^{90,260} Expressed in latently infected cells and in both KS and PEL cells, vCyclin can interact with and phosphorylate cyclin-dependent kinase 6 (Cdk6) to promote cell cycle progression from G₁ to S-phase and accelerate cellular proliferation.^{90,100,175,224,260,376,432}

KSHV uses multiple mechanisms to promote cell survival. The KSHV genome encodes several virus homologues of human antiapoptosis proteins. For instance, vBcl-2 is a KSHV homolog of human antiapoptosis protein Bcl-2.^{98,378} KSHV also encodes several cellular IRF homologues vIRFs that inhibit apoptosis.^{60,148,165,233,259,274,317,390,391} In addition, the KSHV K7 gene encodes a viral inhibitor of apoptosis (vIAP) survivin-ΔEx3 to inhibit apoptosis.⁴⁵⁶ Another unique mechanism that KSHV utilizes to promote tumor growth and cell survival is through activation of the NF-κB pathway. The NF-κB pathway is constitutively active in both KS and PEL,^{21,284} and treatment with inhibitors of NF-κB pathway lead to a complete regression of PEL tumors in a mouse model.²³⁰ Two KSHV genes, vGPCR and vFLIP, have been shown to enhance cell growth and survival by activating NF-κB pathway.^{93,145,270,284,386} vGPCR seems to play an important role in promoting endothelial cell proliferation and transformation.^{18,22,114,182,298,310,339,386,404,405} Endothelial cells ectopically expressing vGPCR have constitutively active VEGF receptors and can proliferate to form both foci in culture and tumors in nude mice independently of VEGF stimulation.^{23,182} KSHV-encoded vIL-6 also promotes cell survival.^{15,202,236,297,308,324,332,453} Finally, it is believed that a variety of cellular growth factors and inflammatory cytokines secreted by KSHV-infected endothelial cells and tumor-interacting stromal cells play a pivotal role in the development of KS. It is well documented that KSHV infection induces the secretion of various growth factors such as IL-6, IL-8, Gro-α, VEGF, and bFGF,^{71,78,282,322,457,484} which could promote cell proliferation through autocrine and/or paracrine signaling. It is important to emphasize that the interaction between HIV and KSHV in AIDS patients plays a significant role in tumor growth. The aggressiveness of AIDS-related KS implicates HIV-1 infection as an important cofactor in rapid KS progression; indeed, the time of KSHV seroconversion until the onset of KS may be years to decades in classic KS while it is only several months in most of the AIDS-related KS cases.^{167,168,291,325,337,355,360} HIV-1 not only activates lytic replication of KSHV²⁰⁶ but also induces secretion of a number of cytokines and growth factor from infected macrophages,^{189,215,256} further promoting tumor cell proliferation and survival, as well as tumor angiogenesis.

Regulation of Angiogenesis—KS tumors are highly angiogenic with abnormally dense and irregular blood vessels. The importance of angiogenesis in KS tumor development is further highlighted by the fact that early stage KS might not yet be a true tumor but a neoplasm of proliferative spindle-shaped cells driven by angiogenesis and inflammation. Angiogenesis is the formation of new blood vessels from existing capillary beds, which, with the exception of wound healing and female reproduction, is a rare event in adults.^{70,150} Pathological angiogenesis, however, correlates with tumor growth and metastasis.¹⁵⁰ Angiogenesis is a complicated process that involves a number of different angiogenic factors. Some angiogenic factors initiate blood vessel remodeling by disrupting the existing blood vessels, while others are responsible for promoting migration, adhesion, and proliferation of endothelial cells for new blood vessel growth and maturation.¹⁵⁰

The mechanisms of KSHV-induced angiogenesis remain to be further elucidated. KSHV-induced angiogenic factors and inflammatory cytokines likely play essential roles. In a SCID

mouse model with human skin grafts, it was demonstrated that VEGF is essential for the inoculated early-stage KS cells to grow into KS-like tumors.³⁷³ Many of the cytokines, including VEGF, bFGF, IL-6, IL-8, GRO- α , TNF- β , and ephrin B2, induced by KSHV infection are angiogenic.^{282,283,322,457,484} Higher levels of serum VEGF were also seen in HIV-1 infected persons with KS compared with HIV-1 infected persons without KS,⁴⁶⁹ and higher mRNA levels of VEGF and angiopoietins, including both Ang-1 and Ang-2, were also detected at higher levels in KS lesions compared to the adjacent normal tissues.⁵⁷ KSHV infection induces expression of cyclooxygenase-2 (COX-2)³²² and heme oxygenase-1,²⁸⁶ both of which are important players in angiogenesis. In addition to the host factors, KSHV vIL-6 expressed during early infection has been shown to stimulate hematopoiesis, plasmacytosis, and angiogenesis.^{15,269,290} A number of KSHV proteins vIL-6, vGPCR, vCCL-1, and vCCL-II have been shown to promote angiogenesis by inducing VEGF expression through different signaling pathways.^{15,41,407,425} vGPCR alone can activate PKC, protein kinase B (PKB), Akt, NF- κ B, and MAP kinases to regulate the expression of growth factors and cytokines.^{18,22,114,298,310,339,386,404} Transgenic mice expressing vGPCR display multi-focal and angioproliferative KS-like lesions.^{189,218,486}

Immune Modulation—Like other viruses, KSHV must evade the host innate immunity that involves type 1 IFNs, phagocytes, natural killer (NK) cells, and complement, as well as the adaptive immune responses that include humoral and cell-mediated immunity. Viral evasion of host immunity not only safeguards virus persistence but also contributes to viral oncogenesis and pathogenesis. KSHV utilizes two major strategies to achieve successful infections. The first is the so-called passive strategy. After a successful entry into host cell, KSHV establishes latency, during which only a minimum number of virus genes are expressed, thus reducing the number of antigens that are exposed to the immune systems. Secondly, during lytic replication or de novo infection, when most viral proteins are expressed and are susceptible to immune surveillance, the virus utilizes an active strategy that involves a number of its own unique genes to modulate the host immune response. Thus, KSHV has evolved multiple mechanisms to not only evade the host immune response but also manipulate existing cytokine regulatory networks to facilitate viral replication and maintenance. In addition to exploiting the cytokine networks, KSHV also expresses genes that modulate the T-cell response, B-cell activation, as well as regulate the complement cascade.

KSHV has a large and complicated genome. It encodes not only proteins necessary for the reproduction and persistence of the virus but also pathogenic factors to promote tumor cell proliferation and survival, regulate angiogenesis, and modulate host immune response in favor of tumor growth (Fig. 1). The function and roles of each of these factors in relation to KSHV-induced malignancy and pathogenesis are further discussed in details.

Functions of KSHV Genes

LANA-1/LNA—In addition to its role in episomal persistence (maintenance, replication, and segregation), LANA-1 is a promiscuous protein that has many cellular interaction partners and modulates p53, STAT3, Rb, and GSK-3 β pathways with integral roles in apoptosis, immune response, development, cell growth, proliferation, and transformation. LANA-1 acts directly or indirectly as a general transcriptional repressor or occasionally as a transcriptional activator. LANA-1 modulation of cellular functions might ultimately contribute to viral latency in KSHV-infected cells.

Much work has been done to determine the role of LANA-1 in KSHV-mediated transformation. In conjunction with the expression of *Hras*, LANA-1 transforms primary rat fibroblasts.³⁵² Overexpression of LANA-1 increases cellular proliferation and lifespan of primary HUVEC.^{399,468} Nevertheless, overexpression of LANA-1 cannot induce anchorage independent

growth, a hallmark of cellular transformation, in NIH3T3 cells, indicating that other viral genes are likely necessary for KSHV-induced malignant transformation.⁴⁶⁸

The mechanism of LANA-1-mediated cellular transformation has been extensively investigated. LANA-1 targets the Rb/E2F pathway and alleviates Rb-mediated transcriptional repression of the E2F pathway.³⁵² LANA-1 upregulates the expression of telomerase by interacting with the Sp1 transcription factor.⁴⁴⁶ In latently infected PEL cells, LANA-1 blocks p53-mediated apoptosis by binding to and inhibiting its transcriptional activity.¹⁵⁴ In KS tumors, apoptosis is not correlated with high expression levels of p53, rather, it is negatively correlated with the expression of LANA-1.²²⁸ LANA-1 inactivation of p53 activity has also been associated with genomic instability.³⁹⁹ HeLa and Rat-1 cell lines stably expressing LANA-1 have increased multinucleation, micronuclei, mitotic bridges, and abnormal formation of centrosomes.³⁹⁹

β -Catenin is overexpressed in PEL cells and KS tumors.^{156–158} Normally, β -catenin is degraded in the cytoplasm by its negative regulator GSK3 β . LANA-1 causes the excess accumulation of β -catenin by binding and relocating GSK3 β to the nucleus where it can no longer regulate β -catenin. Excess β -catenin accumulates and ultimately translocates to the nucleus where it interacts with Tcf/Lef transcription factors to regulate the expression of target genes. β -Catenin targets many genes that have important roles in cell cycle progression, cell growth, and cell proliferation.^{28,50} Notable β -catenin target genes are myc, jun, and cellular cyclin D1.¹⁵⁸

Overexpression of LANA-1 induces the expression of IL-6 by activating the AP-1 pathway.¹² One consequence of the autocrine and paracrine effects of IL-6 signaling is activation of the STAT3 signaling pathway. LANA-1 itself also binds STAT3 in KSHV-infected PEL cells and augments STAT3-induced transcription in reporter assays.³¹⁵

LANA-1 positively and negatively regulates transcription through a variety of mechanisms. In vitro experiments, the N- and C-terminals of LANA-1 repress transcription when fused to a heterologous DNA binding domain.³⁸⁵ Recruitment and interaction with members of the mSin3 transcriptional repressor complex is one mechanism by which LANA-1 represses transcription.²⁴⁴ LANA-1 represses the ATF4/CREB transcriptional activator without interfering with its DNA binding ability.²⁶⁶ LANA-1 inhibits the CBP histone acetyltransferase activity and represses CBP transcriptional activation by preventing its dimerization with c-Fos.²⁴⁴ LANA-1 interacts with a potent transcriptional repressor KLIP1 and relieves its transcriptional repression effect.^{335,496} LANA-1 activates the AP-1 pathway by binding to Jun and facilitating the formation of Jun–Fos heterodimers.¹³ LANA-1 also upregulates Id-1, which is a member of a family of basic helix–loop–helix containing proteins that have key roles in inhibiting cell differentiation, cell cycle regulation, and tumorigenesis.⁴³⁸ Id proteins are expressed at high levels in KS tumor cells, but their roles in KSHV-mediated tumorigenesis are not well understood because LANA-1 induced increases in Id protein expression has no discernable effect on the proliferative capacity of cells.⁴³⁸

LANA-1-mediated transcriptional regulation could contribute to viral latency. LANA-1 form complexes with RBP-J κ to repress RTA expression.²⁴⁷ In addition, LANA-1 interacts with RTA and antagonizes its activation of the RTA promoter.^{247,248} LANA-1 also inhibits transcription of nonlatency-associated genes through its interaction with SUV39H1 and recruitment of HP-1.³⁷¹ SUV39H1 is a histone-H3 methyltransferase. Upon methylation of histone-H3 by SUV39H1, HP-1 is recruited and forms condensed, transcriptionally inactive heterochromatin. Recruitment of these two factors by LANA-1 prompts condensation of the KSHV episome and consequently, transcriptional repression of all viral genes except those

within the latency locus.³⁷¹ Finally, LANA-1 autoregulates its promoter and induces transcription of itself.²¹⁹

vCyclin—The decision to enter into the cell cycle is made in G0/G1 when cells are receptive to growth and differentiation signals.²⁰⁸ Cdks act in combination with cellular cyclins A, D, and E to push cells through the cell cycle.²⁶⁰ The KSHV vCyclin gene encodes a 257 amino acid protein with a molecular weight of 29 kDa. vCyclin has 32% identity and 54% similarity to mammalian cyclin D2 with the homology extending over the full length of the protein.²⁶⁰

vCyclin strongly binds to Cdk6 and weakly binds to Cdk2, Cdk3, Cdk4, and Cdk5; however, only the interaction with Cdk6 has functional significance.^{136,260,279,330} Cdk6 is the catalytic subunit of the protein complex.²¹⁶ vCyclin binds tightly to Cdk6 to form a potent phosphorylation complex that phosphorylates many more targets, including p27KIP1, Id-2, Cdc25a, histone H1, Cdc6, Orc1, and Bcl-2^{260,279,449} than the Cdk6–cellular cyclin D2 protein complex.²⁶⁰ In addition, the vCyclin–Cdk6 protein complex is resistant to many cell cycle checkpoints, which contributes to increased rates of cell proliferation.³³⁰ These two characteristics have important implications for KSHV-infected cells. Increased cellular proliferation, apoptosis,^{330,450} and chromosomal abnormalities⁴⁵⁰ are three main consequences of overexpressing vCyclin.^{136,175,279,376,432} The vCyclin–Cdk6 complex phosphorylates and inactivates Bcl-2, thus contributing to vCyclin-mediated apoptosis.^{330,331}

Rb serves as an important cell cycle checkpoint protein by binding to the transactivation domain of E2F transcription factors to inhibit their functions and prevent cell cycle progression.^{130, 200} Rb interacts with a number of chromosome remodeling proteins like HDAC and the SWI/SNF complex to regulate gene expression.²³⁹ Cdk6–vCyclin phosphorylates and inactivates Rb. Consequently, KSHV-infected cells avoid Rb-induced cell cycle arrest.^{90,175,260}

p27KIP1 is another important regulator of cell cycle. p27KIP1 mutation or inactivity is often associated with poor prognosis in tumor progression. vCyclin can overcome p27KIP1-mediated cell block.^{136,175,279,376,432} When vCyclin is overexpressed in cells, the vCyclin–Cdk6 complex interacts with and phosphorylates p27KIP1 on Thr187 inducing its degradation via the proteasome dependent pathway;^{136,376} however, the situation may be more complicated in vivo. Unexpectedly, p27KIP1 is more highly expressed in PEL cell lines when compared to other lymphomas.^{67,216,376} In PEL cells, the Cdk6–vCyclin complex prevents p27KIP1 from carrying out its function in two ways. First, it forms a stable complex with p27KIP1, thereby sequestering it and preventing it from carrying out its normal function.²¹⁶ Second, the Cdk6–vCyclin complex phosphorylates p27KIP1 on Ser10, which causes p27KIP1 to undergo relocation to the cytoplasm. Upon lytic reactivation, though, the Cdk6–vCyclin complex does induce degradation of p27KIP1 via phosphorylation of Thr187.³⁷⁶ In addition to resistance to p27KIP1 inhibition, Cdk6–vCyclin resistance to cell cycle blocks by checkpoint proteins p16 (Ink4a) and p21Cip1 has also been shown.²⁷⁹

K13/vFLIP—K13 encodes viral FLICE (FADD[Fas-associated death domain]-like IL-1betaconverting enzyme)-inhibitory protein (vFLIP), which is a viral homologue of cellular FLIP proteins.¹²⁸ vFLIP utilizes its death effector domain and TRAF-binding domains to perform two principal functions, inhibition of apoptosis and constitutive activation of the NF-κB pathway. vFLIP is coded by either tricistronic transcripts or a bicistronic transcript that share with to other latent genes LANA-1 and vCyclin.^{125,185,434} The translation of the vFLIP protein is mostly initiated from IRES present in the vCyclin coding region, although a minor amount comes from reinitiation of translation.^{185,272}

In the cytosol, vFLIP interacts with procaspase 8 to reduce the cleavage of procaspase 8 into its active subunits.³² vFLIP also inhibits caspase 3 and caspase 9 like activities in Fas-triggered

A20 cells.³² In addition to its role in inhibiting Fas-induced apoptosis, vFLIP constitutively activates both canonical and noncanonical NF- κ B pathways. vFLIP utilizes its TRAF-interacting domain to interact with the I κ B kinase complex via TRAF2.¹⁸⁸ I κ B sequesters inactive NF- κ B in the cytoplasm.^{20,24} Activation by cytokines induces recruitment of the I κ B kinase complex, composed of IKK α , IKK β , and IKK γ , which phosphorylates and inactivates I κ B.^{20,24} This I κ B inactivation allows NF- κ B to translocate to the nucleus and stimulate the expression of NF- κ B response genes. In PEL cells, vFLIP interacts with the I κ B kinase complex and RIP, a protein kinase that recruits and activates MAPKKK proteins that in turn activate the I κ B kinase complex.^{145,270} Hsp90 is an important member of this protein complex. Treatment of PEL cells with Hsp90 inhibitor ablates NF- κ B activation.¹⁴⁵

The implications of vFLIP-induced constitutive activation of the NF- κ B pathway are significant. NF- κ B activates many mitogenic pathways. Constitutive activation of the NF- κ B pathways has been observed in KSHV PEL cells.^{187,270,284} RNAi-mediated knock-down of vFLIP reduced NF- κ B activity by approximately 80% and sensitized PEL cells to external apoptotic signals, subsequently increasing apoptosis levels.¹⁸⁷ The transforming ability of vFLIP derives from activation of the NF- κ B pathway. Single gene expression studies of vFLIP in a Rat-1 cell line demonstrate that stable vFLIP expression increases cell growth and proliferation, but also facilitates loss of contact inhibition, anchorage independent growth in soft agar assays and induction of tumors in nude mice.⁴²⁹ A20 cells, a murine B-lymphoma cell line, transduced with vFLIP underwent cell proliferation despite constant stimulation with death signals.¹²⁸ Ninety percent of immunocompetent mice injected with these vFLIP transduced A20 cells developed aggressive tumors. As mentioned above, IL-6 is a necessary growth factor for KSHV PEL cells. vFLIP upregulates the expression of cellular IL-6 by activating the JNK/AP-1 pathway.¹⁴ In situ hybridization analysis shows that vFLIP transcripts express at low levels in early KS lesions, but at dramatically higher rates in late stage KS tumors.⁴²⁷ vFLIP expression is inversely correlated with apoptosis.⁴²⁶

K12/Kaposin—Along with the proteins of the latency locus, K12 is expressed in most KSHV-infected spindle tumor cells.²³⁵ Moreover, K12 expression is found in all stages of KSHV tumorigenesis. In advanced spindle cell tumors, K12 expression is detected in approximately 85% of the spindle cells.^{257,311} K12 expression during latency varies from tumor to tumor, and cell line to cell line;²⁵⁷ however, its expression is strongly upregulated in the viral lytic cycle.^{87,413} Initial characterization of the K12 transcript identified a 700 bp gene product that coded for a protein with a predicted molecular weight of 6 kDa, now known as Kaposin.³⁶⁸ Later, detailed transcript analysis determined that the most common mRNA transcript encoded by the K12 locus is actually 1.5–2.3 kb in size.^{235,368} Consequently, the translation program for K12 was determined to be more complex than originally thought, utilizing canonical and alternative translation initiation codons to encode three proteins instead of one.³⁶⁸ These proteins were assigned the names, Kaposin A, Kaposin B, and Kaposin C. While functional characterization of Kaposin A and Kaposin B has been carried out, to date no function has been ascribed to Kaposin C.

Most of the initial characterization on K12 was done with the predominant protein product, Kaposin A.²³⁵ Kaposin A has a predicted molecular weight of 6 kDa; however, it is often detected on Western blots as 16–18 kDa bands and sometimes higher,^{235,312} hinting that the protein undergoes extensive posttranslational modification.³¹² Kaposin A is a highly hydrophobic type II transmembrane protein and is expressed on the cell surface.^{235,311} Initial characterization revealed the transformation nature of Kaposin A. In NIH3T3 and Rat-3 cell lines, overexpression of Kaposin A caused increased foci formation, loss of stress fibers, and loss of contact inhibition.^{235,311} When focally transformed Rat-3 cell lines were injected into nude mice; highly vascular and undifferentiated fibrosarcomas formed within 1–2 weeks.³¹¹ Though the level of transforming activity found in the Rat-3 assay was less than what is

observed in typical cellular and retroviral oncogenes, it was similar to levels found in other herpesviruses.³¹¹ Kaposin A might mediate mitogenic pathways to achieve cellular transformation. Kaposin A activates the ERK-1/2 MAPK pathway and downstream AP-1²³⁵ through its interaction with cytohesin-1, a guanine nucleotide exchange factor that regulates the function of β -integrins. Cells transformed by Kaposin A show elevated activities of cellular serine-threonine kinases such as PKC, CAM kinase I, and MLCK.³¹² Kaposin A possesses a LXXLL nuclear receptor-binding motif. Mutations in this LXXLL motif ablated Kaposin A's transforming ability.³¹²

Most cells that express Kaposin A also express Kaposin B. Kaposin B is a 38 kDa protein⁴⁴² coded by a sequence upstream of the Kaposin A translation initiation site. The Kaposin B transcript utilizes the alternative start codon, CUG, and encodes a series of 23 nucleotide GC rich repeats that vary in different KSHV isolates.^{257,368} Kaposin B upregulates cytokine expression by blocking the degradation of their mRNA transcripts.²⁸⁷ Kaposin B binds to and activates MK2 resulting in the inhibition of U-rich elements (AREs)-mediated mRNA degradation.²⁸⁷

K15—K15 has a complex expression profile.¹⁰³ Isolates from BCBL-1 cells show differentially spliced protein products ranging from 281 to 489 aa in length, and 23–55 kDa in size that localize to the endoplasmic reticulum, mitochondria, and plasma membrane surface.^{103,395} K15 can also undergo proteolytic cleavage.³⁹⁵ K15 is weakly expressed during latency, but is strongly upregulated in viral lytic cycle.⁴⁷⁶ K15 promoter is activated by RTA.^{103,174,476} Although there is no sequence homology, K15 has the same structural characteristics as EBV LMP2A including a highly hydrophobic N-terminus, a variable number of transmembrane domains, and a C-terminus containing motifs with high sequence identity to putative SH2 and SH3 src kinase binding domains.^{52,103,476} Unlike LMP2A, the cytoplasmic domain of K15 does not possess signal transduction capability even though the domain is readily phosphorylated¹⁰³; however, like LMP2A, it inhibits B-cell receptor (BCR) activation.¹⁰³ K15 has been shown to localize in the lipid rafts, common carriers of signal transducers like BCR.⁵² The K15 C-terminus binds TRAF-1, TRAF-2, and TRAF-3.^{52,174} K15 interaction with TRAF-2 strongly activates the NF- κ B pathway and the AP-1 transcription factor through the JNK1 and ERK MAP kinase.⁵² All K15 spliced variants have a common C-terminus and high sequence variation in the N-terminal hydrophobic regions.^{52,103,476} Even though the C-terminus cannot function as a signal transducer, phosphorylation in its SH2 domain has been detected.⁵²

Viral Interferon Regulatory Factors—KSHV encodes three homologues of human IFN regulatory factors (vIRFs) including vIRF, vIRF-2 encoded by K11.1, and vIRF-3 or LANA-2.^{61,165,300,362} Cellular IRFs are known to participate in IFN signal transduction. The diverse cellular effects of IFN, including tumor suppression through induction of p21 and histone H4 gene, induction of apoptosis, upregulation of MHC class I and II antigen expression, and regulation of the natural killer cell development, are mediated directly by IRFs or indirectly through interaction with various cellular factors including STAT proteins, p300/CBP, and NF- κ B.^{203,278,307} The most common IRF-targeting promoter sites are ISRE, GAS, PRD-I, PRD-II, PRD-III, PRD-IV, and NF- κ B-binding sites. Some IRFs positively regulate the transcription of IFN-responsive genes^{53,196,344,369} while others negatively regulate IFN signaling.^{470,471} For example, IRF-1 and IRF-2 compete for the identical ISRE, accounting for their antagonistic activities.¹⁹⁶ IRF-1 positively reinforces IFN- β signal transduction, whereas IRF-2 is a negative regulator. Furthermore, IRF-1 is a tumor suppressor while IRF-2 is an oncogene.^{196,436,437} IRF-1 overexpression promotes cell cycle arrest through p53-independent pathways by direct induction of p21.^{435,436} IRF-2 overexpression inhibits these IFN-mediated effects leading to cellular transformation and tumor formation in nude mice.¹⁹⁷ vIRF is the first KSHV oncogene identified.¹⁶⁵ Overexpression of vIRF in rodent fibroblast cells causes cellular

transformation and downregulation of p21 and MHC class I antigen through the inhibition of cellular IFN signal transduction pathways.^{148,165,259,503} In this regard, vIRF behaves similarly to IRF-2. vIRF has also been shown to be a transcriptional regulator and regulates the expression of other KSHV genes.^{259,364} vIRF probably achieves these functions through interactions with cellular IRF-1, IRF-3, ICSBP, p300, and CBP.^{60,165,258,267,319,389} It appears that vIRF represses the IFN antiviral response by blocking IRF-3 recruitment of the CBP/p300 coactivators.²⁶⁷ Furthermore, vIRF interacts with p53, and inhibits p53-dependent apoptosis.^{317,391} vIRF also autoactivates its own expression through two *cis*-elements, named *Vac1* and *Vac2*, in the vIRF promoter that do not contain any ISRE-like sequences and are unresponsive to induction with IFN- α/β .⁴⁶⁵ Thus, vIRF might be able to target other viral and cellular genes in an IFN-independent mechanism. vIRF is an early lytic gene expressed in KS lesions.^{127,467} Although the expression of vIRF is significantly increased by TPA, low level of vIRF expression is also detected in uninduced KSHV-infected cell lines which may be either due to the presence of a minor latent transcript or an undefined expression mechanism of regulation that is not tied to viral lytic replication.^{96,467} The control of vIRF expression during latency is mostly mediated by a transcriptional silencer *Tis* in the vIRF promoter.⁴⁶⁶ Similar mechanisms of regulation may also be present for other KSHV lytic genes in addition to LANA-1-mediated gene repression.

vIRF-2 encodes a protein of 18 kDa. Similar to vIRF, vIRF-2 does not bind to ISRE, rather it binds to the NF- κ B-binding site.⁶¹ vIRF-2 interacts with IRF-1, IRF-2, ICSBP, RelA, and p300 but not IRF-3 in vitro. Consequently, vIRF-2 inhibits the IRF-1- or IRF-3-mediated transcriptional activation of IFN- α promoter as well as RelA-stimulation of HIV LTR.⁶¹ vIRF-2 inhibits the antiviral effect of IFN by interacting with (double-stranded RNA-activated protein kinase) PKR and inhibiting its autophosphorylation, and the phosphorylation of PKR substrates histone 2A and eukaryotic translation initiation factor 2 α .⁵⁹ Interestingly, vIRF-2 is expressed at low levels in BCBL-1 cells and is not induced by TPA, suggesting that it may be a latent gene.⁵⁹ The expression profile of vIRF-2 in KS lesions is unknown.

LANA-2 is abundantly expressed in the nuclei of PEL cells and has been described as a latent gene. However, because its expression levels can be greatly increased following TPA treatment, and is not expressed in KS tumors, whether it is truly latent remains controversial.^{274,362} LANA-2 interacts with p53 to mediate gene transcription, and recruits IRF3 and IRF7 to inhibit IFN signaling.^{274,362}

vGPCR—vGPCR is a 7-transmembrane, IL-8 receptor homologue that constitutively signals several pathways downstream of multiple G protein subunits in a phospholipase C-and phosphatidylinositol 3-kinase (PI-3K)-dependent manner.⁶⁵ Signaling through PKC, PKB, Akt, NF- κ B, and MAPK pathways increases expression of genes involved in cellular proliferation, cell survival, and transformation, tendering vGPCR as one of the potential key factors involved in KSHV-induced malignancies.^{18,22,114,183,298,299,310,339,386,404,406,407} vGPCR increases expression of a number of autocrine and paracrine cytokines and growth factors such as IL-1 β , IL-6, IL-8, GM-CSF, TNF- α , bFGF, Gro- α , VEGF, and MCP-1, which might be essential for early KS cell proliferation and KS tumor angiogenesis and inflammation.^{22,299,339,386,396,407} Thus, vGPCR may contribute to KS development via an autocrine and paracrine mechanism albeit it is a viral lytic gene. Expression of vGPCR in endothelial cells leads to constitutive activation of VEGF receptor and cell immortalization,^{23,183,406} and transgenic mice expressing vGPCR developed highly vascular “KS-like” lesions.^{218,486} Interestingly, vGPCR may also regulate the expression of both latent and lytic genes.^{64,421}

vIL-6—vIL-6 is a viral early gene. As a homologue of cellular IL-6, vIL-6 can stimulate multiple cellular pathways to promote cellular proliferation, cell survival, and extrahepatic acute-phase response through engagement of the gp130 coreceptor independently of IL-6

receptor gp80.^{104,202,236,297,300,308,324,332,453} vIL-6 also plays an important role in KSHV immune modulation, protecting PEL cells from IFN- α -induced antiviral response.⁹² In addition, vIL-6 induces the secretion of cellular IL-6 and VEGF to support cell growth of IL-6-dependent cells, and contribute to hematopoiesis, tumorigenesis, and angiogenesis.^{15,153,159,269,305}

K1 (KIS)—K1, the first ORF in the KSHV genome, encodes a type 1 membrane glycoprotein that is significantly induced during viral lytic replication.^{254,448} K1 can activate B cells and induce inflammatory cytokines to regulate immune responses.²⁵⁴ K1 promotes cell growth and causes immortalization of primary endothelial cells.^{255,460} Expression of K1 in rodent fibroblasts produces morphological changes and foci formation, characteristics of cellular transformation.²⁵⁵ K1 transgenic mice develop sarcomas and plasmablastic lymphomas and display constitutive activation of NF- κ B, Oct-2, and Lyn.³⁴⁹ In addition, it has been shown that K1 can induce matrix metalloproteinase-9 and VEGF in endothelial cells,^{457,461} two factors implicated in angiogenesis and cell invasion.

K7/vIAP—vIAP is a homolog of the cellular protein survivin- Δ Ex3 and is not found in any other herpesviruses. Both the viral and cellular survivin- Δ Ex3 contain a conserved BH2 domain and a partial IAP repeat domain.⁴⁵⁶ vIAP is a 19–21 kDa glycoprotein that localizes to the host cell mitochondrial membrane and inhibits apoptosis induced by the Fas and TRAIL pathways, Bax, TNF- α and cycloheximide, staurosporine, and ceramide.^{143,456,490} vIAP protects KSHV-infected cells from apoptotic death in two distinct ways. First, it enhances cytosolic Ca²⁺ influx and prevents mitochondrial damage.¹⁴³ Second, it acts as protein bridge between the host mitochondrial protein Bcl-2 and caspase 3 to effectively suppress caspase 3 function.⁴⁵⁶

MIR-1/K3 and MIR-2/K5—Two similar proteins MIR-1 and MIR-2 have been shown to actively prevent the expression of cell surface MHC Class I antigen that serve to alert the cytolytic T-lymphocytes (CTLs), the main protagonists of virus elimination.^{110,111,214} Most virus-specific CTLs are CD8⁺ T cells that recognize cytosolic, usually endogenously synthesized, viral antigens in association with Class I MHC on any nucleated cell. MIR-1 and MIR-2, expressed during lytic replication and localized at the endoplasmic reticulum (ER), negatively modulate the CTLs-dependent immune response by triggering endocytosis of the surface MHC Class I molecules for degradation.^{110,214} This function of MIR-2 is specific for human leukocyte antigen (HLA)-A and HLA-B, which are responsible for presenting antigens to CTLs, and to a lesser extent, HLA-E, but not HLA-C.^{110,214} In contrast to MIR-2, MIR-1 downregulates HLA-A, -B, -C, and -E.²¹⁴ Consequently, KSHV-infected cells expressing reduced levels of MHC Class I molecules, are deficient in antigen processing and presentation, and are therefore less susceptible to CTL killing.⁴⁹ In addition, MIR-2 also reduces the expression of molecules involved in T-cell activation, reducing the visibility of KSHV-infected B cell to T-helper cells, thereby decreasing T-cell responses, cytokine release and the production of co-stimulatory signals for CTL generation.¹¹¹ Both MIR-1 and MIR-2 may also help KSHV evade natural killer cell immune responses, which cause immediate killing of virus-infected cells through exocytosis of perforin- and granzyme-containing granules and secreting cytokines, mainly IFN- γ , to activate CTLs and macrophages.^{213,375}

vCCL-1, vCCL-2, and vCCL-3—vCCLs are three KSHV lytic proteins formerly known as vMIPs. vCCL-1 (K6), vCCL-2 (K4), and vCCL-3 (K4.1) share 25–40% homology with human MIP-1 α (macrophage inflammatory protein 1 α) α 1CC chemokine.^{300,324} Chemokines are molecules that interact with G-protein coupled chemokine receptors and recruit leukocytes to sites of inflammation, and also are involved in angiogenesis, haematopoiesis, and lymphocyte development.^{4,102,271,313,314} All three vCCLs are able to induce angiogenesis in the chorioallantoic membranes of chicken eggs⁴¹ suggesting that they may act synergistically with

host factors such as VEGF, bFGF, and IL-6 to promote the abnormal angiogenesis in KS lesions. vCCL-1 is able to bind to a broad range of chemokine receptors including CCR1, CCR2, CCR5, CXCR4, and CX3CR1.²³⁴ vCCL-1 may act as a competitive antagonist with the host chemokines, since it does not induce a Ca^{2+} influx after binding these receptors. In vitro, vCCL-1 blocked the chemoattractive properties of host CC and CXC chemokines,^{41, 97,234,300} while in a rat model, vCCL-1 suppressed the host inflammatory response and decreased the infiltration of inflammatory leukocytes.⁹⁷ vCCL-1 and vCCL-2 bind to CCR-8, and vCCL-1 is able to induce the secretion of VEGF-A in PEL cells.²⁶⁹ Both vCCL-1 and vCCL-2 are able to block dexamethasone-induced apoptosis in PEL cells.²⁶⁹ vCCL-3 binds to CCR-8 and CCR-4, and has been shown to be selectively chemoattractant for Th2 cells.⁴²⁵ KSHV vCCLs can polarize the adaptive immune response toward a predominantly Th2-type (i.e., humoral) response at sites of KSHV infection, potentially reducing the efficacy of the antiviral response.

KCP (ORF4)—Complement bridges both innate and adaptive immune responses and humoral and cell-mediated immunity. The ORF4-encoded complement-control protein (KCP) inhibits the activation of the complement cascade.^{309,417–419} KCP is also associated with the envelope of purified KSHV virions where it potentially protects them from complement-mediated immune response.⁴¹⁸

K14 (vOX2)—vOX2 is a homolog of the cellular protein OX2, a glycosylated cell surface protein and member of the immunoglobulin superfamily that restricts cytokine production in a paracrine fashion. vOX2 has structure similar to cellular OX2; however, in contrast to cellular OX2, it potently activates inflammatory cytokine production.¹⁰⁵ vOX2 induces the production of IL-1 β , TNF- α , and IL-6 from various cell types, including monocytes/macrophages, and dendritic cells, and cooperates with IFN- γ in a paracrine manner to induce cytokine production in a B-cell line.¹⁰⁵

vBcl-2 (ORF16)—vBcl-2 is a viral lytic protein expressed in both spindle cells and monocytes in KS lesions.^{378,475} vBcl-2 only displays 15–20% amino acid identity to cellular Bcl-2, but it contains the critical BH1 and BH2 domains required to heterodimerize with cellular Bcl-2, and potently suppress caspase 3 death effector functions.^{98,378} vBcl-2 is an even more potent suppressor of apoptosis than its cellular homolog, Bcl-2. vBcl-2 has been shown to prevent apoptosis induced by vCyclin, and unlike cellular Bcl-2, vBcl-2 cannot be converted to a pro-apoptotic form by caspase-mediated cleavage.^{33,98}

SUMMARY

KSHV has been established as the causative agent of KS, PEL, and MCD, malignancies occurring more frequently in AIDS patients. The aggressive nature of KSHV in the context of HIV infection suggests that interactions between the two viruses enhance pathogenesis. KSHV latent infection and lytic reactivation are characterized by distinct gene expression profiles, and both latency and lytic reactivation seem to be required for malignant progression. As a sophisticated oncogenic virus, KSHV has evolved to possess a formidable repertoire of potent mechanisms that enable it to target and manipulate host cell pathways, leading to increased cell proliferation, increased cell survival, dysregulated angiogenesis, evasion of immunity, and malignant progression in the immunocompromised host.

Worldwide, approximately 40.3 million people are currently living with HIV infection.² Of these, a significant number are coinfecting with KSHV.^{118,129,381} The complex interplay between the two viruses dramatically elevates the risk for development of KSHV-induced malignancies, KS, PEL, and MCD. Although HAART significantly reduces HIV viral load, the entire T-cell repertoire and immune function may not be completely restored.⁹⁹ In fact,

clinically significant immune deficiency is not necessary for the induction of KSHV-related malignancy.⁸¹ Because of variables such as lack of access to therapy, noncompliance with prescribed treatment, failure to respond to treatment and the development of drug-resistant strains of HIV, KSHV-induced malignancies will continue to present a major health concern.

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Figure 1. KSHV genome and genes. The names of genes are labeled in color according to gene function (immunomodulation in blue, mitogenic and cell cycle in purple, antiapoptosis in green, and viral structure and replication in black). The blocks representing the ORFs are also labeled in color according to gene class (immediate-early in orange, early in light blue, late in red, latent in green, and unclassified in white). (See Color Plates)

Figure 2. Transcription of the latency-associated region of the KSHV genome. The KSHV latency-associated region encodes four proteins, indicated by black boxes, as well as 12 miRNAs (white boxes) and is flanked by lytic genes (gray boxes). Two latent promoters (white arrows), splice sites, and poly(A) addition sites are indicated. Sequence coordinates are derived from the prototype BC-1 KSHV genome (GenBank accession number NC_003409). Figure is modified from reference ⁷³.