Published in final edited form as:
Adv Virus Res. 2010 ; 78: 87–142. doi:10.1016/B978-0-12-385032-4.00003-3.

Molecular Biology of Kaposi's Sarcoma Herpesvirus and Related Oncogenesis

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Abstract

Kaposi's sarcoma herpesvirus (KSHV), also known as human herpesvirus 8 (HHV-8), is the most recently identified human tumor virus, and is associated with the pathogenesis of Kaposi's sarcoma and two lymphoproliferative disorders known to occur frequently in AIDS patients—primary effusion lymphoma and multicentric Castleman disease. In the 15 years since its discovery, intense studies have demonstrated an etiologic role for KSHV in the development of these malignancies. Here, we review the recent advances linked to understanding KSHV latent and lytic life cycle and the molecular mechanisms of KSHV-mediated oncogenesis in terms of transformation, cell signaling, cell growth and survival, angiogenesis and immune invasion, and highlight the potential therapeutic targets for blocking KSHV tumorigenesis.

I. GENERAL BACKGROUND

A. Discovery of KSHV/HHV-8

Kaposi's sarcoma (KS) was first described by a Hungarian dermatologist, Moritz K. Kaposi, in 1872 (Kaposi, 1872). Kaposi published the case histories of elder male patients in Vienna with "idiopathic multiple pigmented sarcoma of the skin" which is now referred to as classic KS (Antman and Chang, 2000). Prior to the acquired immunodeficiency syndrome (AIDS) epidemic, KS was thought of as a rare, slow progressing neoplasm which affects mainly elderly men of Mediterranean and Eastern European region. However, the AIDS epidemic triggered KS to become the most aggressive AIDS-associated cancer which can present with lymphoadenopathy rather than skin lesions (Oettle, 1962). Unlike classic KS, this endemic KS often can be rapidly fatal and is associated with significant morbidity and mortality, and is now recognized as one of the leading cancers in African children with HIV (Bayley, 1984; Downing *et al.*, 1984). Importantly, KS is also known to develop after organ transplantation (posttransplant or iatrogenic KS; Penn, 1983). The fact that the immunosuppressed patients born in countries where classic KS occurs continues to develop KS after a transplant suggests that there is a genetic predisposition or an infectious agent transmitted and responsible for KS development. Studies of AIDS case surveillance showing that KS occurs predominantly in gay and bisexual men with AIDS instead of AIDS patients with hemophilad or intravenous drug users further support the existence of an infectious cofactor (Beral *et al.*, 1990).

According to the epidemiological data, several groups set out to identify a "KS agent" in the early 1990s. In 1994, Chang and Moore's group successfully identified the infectious cause of KS as a new herpesvirus called Kaposi's sarcoma-associated herpesvirus (KSHV) using polymerase chain reaction-based subtractive analysis between the KS lesions and unaffected skin from the same patient (Chang *et al.*, 1994). Analysis of conserved herpesviral genes

showed that KSHV belongs to a clade of primate herpesviruses within the gamma2 sublineage, and it is ranked eighth known human herpesvirus (HHV-8) which is closely related to rhesus rhadinovirus (RRV) in nonhuman primates and was with their hosts ~25 million years ago (McGeoch and Davison, 1999).

B. Diseases associated with KSHV

In the several years since the original identification of KSHV from KS lesions by Chang and Moore, KSHV sequence has been described in an array of disease entities. They are included marrow hypoplasia, haemophagocytic syndrome (HPS), multiple myeloma, sarcoidosis, angio-immunoblasticlymphoma, and most recently primary pulmonary hypertension (PPH; Cool *et al.*, 2003; Low *et al.*, 1998; Pastore *et al.*, 2000; Schulz, 2006). Since these results are largely based upon PCR analysis for detection of KSHV DNA which can be froth with false positivity, and none of these findings have been confirmed by several other investigating groups, it is still yet to be accepted that KSHV plays a significant role in any of these diseases. However, KSHV has been demonstrated to be present in endothelial/spindle cells and the cells that appear to constitute the primary derivation of the tumor (Boshoff *et al.*, 1995). In addition to KS, two B-lymphocyte disorders: multicentric Castleman's disease (MC; Soulier *et al.*, 1995) and primary effusion lymphoma (PEL; Cesarman *et al.*, 1995) are consistently linked with KSHV infection.

1. Kaposi's sarcoma—KS is an unusual multifocal neoplasm characterized by dark purple lesions, which differs from most other common tumors in that the lesions contain multiple cell types (Boshoff *et al.*, 1997). KS lesions contain extensive neoangiogenesis, infiltrating inflammatory cells, erythrocyte extravasation, endothelial cells, and "spindle" cells typical for KS. There are four distinct clinical variants of KS which is based on the extent of immunosuppression and severity of infection. These include classic KS, endemic KS, iatrogenic KS, and AIDS-associated KS (Boshoff and Chang, 2001). The form of KS that was originally described by Kaposi is now referred to as classic KS. Classic KS most commonly presents in HIV-negative elderly male patients of Mediterranean and Eastern European decent and is relatively indolent (Franceschi and Serraino, 1995). Endemic KS is the prevalent form of the disease in Equatorial, Eastern, and Southern Africa, and is a substantially more aggressive form than classic KS (Wabinga *et al.*, 1993). Unlike classic KS, endemic KS often presents in HIV-negative children as a lymphadenopathy rather than skin lesions (Ziegler and Katongole-Mbidde, 1996). Latrogenic or posttransplant KS is developed in patients undergoing immunosuppressive therapy to prevent graft rejection after organ transplantation (Regamey *et al.*, 1998). The most aggressive form of KS is the AIDS-associated KS, which is the most common neoplastic manifestation of AIDS in the United States and Europe (Martin *et al.*, 1993). This form of KS is most commonly presented in gay and bisexual men, suggesting that the disease transmission is likely through high-risk sexual routes (Gao *et al.*, 1996b; Kedes *et al.*, 1996; Simpson *et al.*, 1996). Distinct from the classic form of KS localized to the lower extremities; AIDS-KS commonly occurs throughout the body, which includes skin of face, torso, the extremities, and mucous membranes of the oral cavity (Cheung, 2004). However, despite these different clinical manifestations of KS, the histology of KS lesions from skin, lymph nodes, respiratory tract, and intestines are very similar.

2. Primary effusion lymphoma—PEL, also referred to as body cavity-based lymphoma (BCBL), is a rare, rapidly fatal lymphoma associated with KSHV infection and commonly found in HIV-infected patients (Cesarman, 2002). PEL is a unique form of NHL found more commonly in immunocompromised AIDS patients and unlike KS, PEL is generally presented as a pleural or pericardial effusion without a detectable tumor mass (Carbone and Gaidano, 1997), or can present as a solid mass in the lymph nodes, lungs, or the

gastrointestinal tract (Arvanitakis *et al.*, 1996). Due to the presence of hypermutated immunoglobulin genes and markers of late stage B cell differentiation like CD30 and CD138, PEL cells are thought to be usually monoclonal and originated from postgerminal center B cells (Arvanitakis *et al.*, 1996; Carbone *et al.*, 1997; Gaidano *et al.*, 1996). In PEL cells, it has frequently been seen that KSHV presents as single positive or KSHV/Epstein Barr Virus (EBV) double positive, and that the KSHV genome is maintained at a relatively high copy number (50–150 per cell; Arvanitakis *et al.*, 1996; Cesarman *et al.*, 1995; Renne *et al.*, 1996a).

3. Multicentric Castleman's disease—Multicentric Castleman's disease (MCD) is a usual lymphoproliferative disorder characterized by expanded germinal centers with B cell proliferation and vascular proliferation. KSHV-positive MCD is now recognized as a distinct subset of MCD, called plasmablastic MCD, which contains large plasmablastic cells (Dupin *et al.*, 2000). Dysregulated IL-6 levels are considered a likely contributor to the clinicpathophysiology of MCD (Parravicini *et al.*, 1997). Like KS and PEL, KSHV genomes are detectable in almost all HIV-seropositive MCD cases and approximately 50% HIV-seronegative MCD cases (Dupin *et al.*, 1999; Soulier *et al.*, 1995). However, different from PEL cells, coinfection of EBV with KSHV has not been detected in MCD plasmablasts.

C. Epidemiology of KSHV infection

Seroepidemiologic studies have clearly shown that KSHV is prevalent throughout the world, although there appears to be striking variation in local seroprevalence. The association between KS prevalence and KSHV seroprevalence is high. In an attempt to understand the divergence and preference of KSHV in certain human populations, several groups have been working on the pattern of KSHV variability (Alagiozoglou *et al.*, 2000; Biggar *et al.*, 2000; Lacoste *et al.*, 2000; Poole *et al.*, 1999). Unlike other herpesvirus, KSHV contains a highly variable gene K1 which is located at the region next to the terminal repeat (TR) in viral genome. This makes it be a good marker to trace KSHV variants that are associated with particular populations. Based on the phylogenetic analysis of K1 gene, KSHV has been classified into five main branches (termed A–E) which appears to relate with different human populations (see Table 1). Generally, the sequence variation between these different clades is very low and less than 3% at nucleotide level in most regions of the viral genome. In view of the fact that KSHV is highly coevolved with the human population, the geographical distribution would be interesting to further investigate. In 1996, the antibodies produced by recombinant capsid protein or the latent nuclear antigen (LANA) made it possible to study the distribution of KSHV seroprevalence among the different risk groups (Gao *et al.*, 1996a,b; Kedes *et al.*, 1996; Lennette *et al.*, 1996; Simpson *et al.*, 1996). The epidemiology data showed that KSHV remains widespread in sub-Saharan Africa, where KSHV is found in more than 50% of adults (Simpson *et al.*, 1996), and relatively frequent in countries from the Mediterranean region which ranges from 3% of northern Italy to 30% in Sicily (Calabro *et al.*, 1998; Whitby *et al.*, 1998). In contrast, seroprevalence rates are lower than 5% in northern Europe, Asia, and most parts of North America. In endemic areas like Africa, it has been found that transmission from the mother to the child or among siblings or transmission through sexual contact is the most important route (Eltom *et al.*, 2002; Martin *et al.*, 1998; Simpson *et al.*, 1996). However, in nonendemic areas, KSHV is commonly found in persons who have multiple sexual partners (especially homosexual men) or who immigrate from endemic areas (Dukers *et al.*, 2000; Melbye *et al.*, 1998). Although KSHV transmission by blood transfusion or transplanted organs is documented, based on cost-analysis most countries do not yet routinely screen blood or organ donors for KSHV infection (the epidemiological studies related to KSHV transmission are reviewed elsewhere; Corey *et al.*, 2002; Henke-Gendo and Schulz, 2004).

II. LIFE CYCLE OF KSHV

KSHV, like other herpesviruses, exhibits a biphasic life cycle with predominant lifelong latent infection and a typical short-lived lytic reactivation cycle. Latent infection is the quiescent state of the viral life cycle, which is characterized by the expression of a limited number of viral genes with no production of virus particles. Majority of the herpesviruses other than the members of gamamaherpesvirus (KSHV and EBV) family do not cause any obvious pathology during latent infection. Members of the gammaherpesvirus have the ability to drive cell proliferation and transformation and are broadly referred to as oncogenic viruses. Kaposi's sarcoma-associated herpesvirus is the latest member of the human herpesviruses, which belongs to the gammaherpesvirus subfamily, rhadinovirus genera and have a significant genetic similarity with EBV, a member of the lymphocryptovirus genera (see reviewed in Damania, 2004). Full genome sequence of KSHV virus from KS biopsy samples and PEL cells reveal that its genome is approximately 165 kbp in size with a central region of low GC (L-DNA) flanked by GC-rich (H-DNA) TR units (Neipel *et al.*, 1997b; Russo *et al.*, 1996). The L-DNA is the viral protein-coding region, which encodes for at least 90 ORFs, some with homology to cellular genes (Neipel *et al.*, 1997a,b; Russo *et al.*, 1996; Fig. 1). These viral homologs seem to be the pirated copies of the human genome, which were acquired during the process of evolution by the viruses to have growth and immune evasion advantages (Moore and Chang, 1998a,b; Neipel *et al.*, 1997a,b). The past 15 years of research have certainly advanced our understanding of the biology and pathogenesis of KSHV.

The KSHV genome exists as linear dsDNA copy in the virion particle. It is delivered into the infected cells by a mechanism which is likely to be a multistep process which is yet to be completely resolved (Chandran, 2010). The virion particle attaches to the host cell surface by temporal interaction of multiple cellular receptors with surface glycoproteins. Attachment is followed by penetration of the viral capsid into the cytosol, achieved by either direct fusion of the virion envelope with the plasma membrane or by internalization through endocytosis through fusion of viral envelope with endosomal membrane (reviewed in Chandran, 2010). Virion capsid delivered to the cytoplasm is transported to the nuclear periphery, which is followed by disassembly of virion capsid and release of viral DNA into the nucleus (Naranatt *et al.*, 2004, 2005; Raghu *et al.*, 2007). The entry of virion into the targets' cells also brings cellular and viral proteins as well as RNA (Bechtel *et al.*, 2005a,b; Zhu *et al.*, 2005). These proteins include replication and transcription activator (RTA), ORF8, ORF21, ORF24, ORF25, ORF26, ORF33, ORF75, and heat shock proteins 70 and 90 (Bechtel *et al.*, 2005b; Zhu *et al.*, 2005). These proteins are considered to be important in establishing early infection. Since RTA is an immediate early protein, the incoming RTA may boost lytic replication and increase the viral copy number. A quantitative real-time PCR analysis of the early transcripts detected RTA as early as 2 h postinfection, which declines sharply at 24 h postinfection (Krishnan *et al.*, 2004). In contrast, expression of ORF73 encoded LANA is detected at very low levels within 6 h postinfection but the levels increase significantly 24 h postinfection (Cai *et al.*, 2007; Lan *et al.*, 2005). Newly synthesized and virally delivered RTA promotes expression of LANA by binding to the LANA promoter (Lan *et al.*, 2005). Expression of LANA subsequently blocks the expression of lytic proteins and pushes the cells to enter into latent phase. Fine tuning of LANA and RTA expression levels decides the fate of the virus which undergoes the latent to lytic cycle (Lan *et al.*, 2005). The distinct viral gene expression profiles during latent and lytic phase of the viral life cycle will be discussed in following sections.

A. Latent infection

Latency is characterized by the expression of subset of viral transcripts and persistence of the viral genome as a circular episome attached to the host chromatin. Another characteristic

feature of latency is that the cells harboring the viral genome downregulate cell surface makers which can be typically detected by the host immune surveillance. Importantly, viral-encoded latent genes have been shown to play an important role in modulating viral and cellular gene expression to successfully establish latent infection.

1. KSHV latent genes/transcripts—Due to the lack of a true latency animal model for studying KSHV infection, cell lines derived from KSHV-infected patients have proved useful in characterizing the expression profiles of latency-associated genes (Cannon *et al.*, 2000; Flore *et al.*, 1998; Foreman *et al.*, 1997; Renne *et al.*, 1996b). PEL cells, which maintain high levels (98–99%) of latently infected cells (a fraction of KSHV-infected cells can undergo spontaneous lytic reactivation) restrict transcription to specific viral genes, including the latency-associated nuclear antigen encoded by ORF73, viral cyclin D encoded by ORF72, vFLIP encoded by ORF71, Kaposin encoded by K12, and viral miRNA (Burysek and Pitha, 2001; Dittmer *et al.*, 1998; Kedes *et al.*, 1997; Rainbow *et al.*, 1997; Sadler *et al.*, 1999). Another latent protein that consistently detected in KSHV-induced tumors is viral interferon regulatory factor (vIRF; Russo *et al.*, 1996). Genes encoded by ORF71, ORF72, and ORF73 are expressed from the same locus in polycistronic, differentially spliced mRNAs whose transcription is regulated by a common promoter upstream of LANA (Dittmer *et al.*, 1998; Grundhoff and Ganem, 2001). Interestingly, LANA promoter is bidirectional and also controls the transcription of ORF73, 72, and 71 during latency and a bicistronic transcript encoding the expression of K14 and ORF74/vGPCR during lytic cycle (Chiou *et al.*, 2002). Intriguingly, the bicistronic transcripts for ORF74-K14 were detected in some KS lesions and latent biopsy samples. However, it is somewhat enigmatic that ORF74-K14 can be expressed in latently infected cells that coexpress LANA–vCyclin–vFLIP from the same locus (Jeong *et al.*, 2001; Nador *et al.*, 2001). In addition, the Kaposin is expressed from the promoter present downstream of ORF73 (Li *et al.*, 2002). Among these latent proteins, LANA is the most consistently detected antigen in KSHV-infected cells of KS, PELs, and MCD origins and is a hallmark of KSHV genome persistence (Ballestas *et al.*, 1999; Cotter and Robertson, 1999; Dupin *et al.*, 1999). LANA is a large (220–230 kDa) heavily posttranslationally modified nuclear protein detected as specific punctate dots in immunofluorescence assays (Lennette *et al.*, 1996). Colocalization of these LANA punctate dots with the hybridization signals for the KSHV genome by immnuo-FISH (fluorescence *in situ* hybridization) assay in the chromosomes of the infected cells suggested a role for LANA in viral genome attachment to the host chromatin (Cotter and Robertson, 1999). Studies from a number of laboratories later identified LANA binding sites (LBS) in the KSHV genome, which mapped to the TR units (Ballestas and Kaye, 2001; Cotter *et al.*, 2001). In addition, binding of LANA to the TR DNA was mapped to the DNA-binding domain of LANA at the carboxyl terminus (Cotter *et al.*, 2001; Hu and Renne, 2005).

2. KSHV latent replication and persistence—Linear KSHV genome circularizes to make episomal DNA through a not-yet-known mechanism upon entry into the nucleus following infection. The viral genome persists as a circular episome in the form of highly ordered chromatin structure during latent infection (Stedman *et al.*, 2004, 2008). LANA has been shown to be important for attaching the viral episomal structure to the host chromatin. The amino-terminal domain of LANA has a chromatin binding sequence (5–22 aa) that attaches to chromatin surface by binding to a multiprotein complex including histones on the cellular chromatin (Barbera *et al.*, 2006; Cotter and Robertson, 1999; Krithivas *et al.*, 2002; Lim *et al.*, 2003; Matsumura *et al.*, 2010; Ottinger *et al.*, 2006). The carboxyl terminal domain of LANA directly binds to the LANA binding sequence (LBS) located in the TRs of the viral genome (Cotter *et al.*, 2001; Hu and Renne, 2005; Komatsu *et al.*, 2004; Srinivasan *et al.*, 2004). Binding of LANA at the TR is critical to efficient initiation of latent replication

at the TRs as demonstrated by short-term replication assays using a construct with the TR cloned onto a plasmid (Hu *et al.*, 2002; Komatsu *et al.*, 2004; Lim *et al.*, 2002; Verma *et al.*, 2006). In an attempt to identify the minimal DNA element required for replication at the TR, Hu *et al.* performed short-term replication assays with the deletion mutants of the TR and mapped a 71-bp unit of the TR as the minimal replicator element (Hu and Renne, 2005). This unit comprises LBS1/2 and an adjacent 29- to 32-bp-long GC-rich element referred to as replication element (RE) upstream of the LBSs (Hu and Renne, 2005). We recently identified a latent replication origin in the long unique region of the viral genome, which initiates replication independent of viral proteins in trans, suggesting that this is an autonomously replicating element in the LUR (Verma *et al.*, 2007a). In contrast to the LANA-dependent replication origin of TR, this autonomously replicating element is high in AT content and can recruit the host cellular replication machinery to initiate replication (Verma *et al.*, 2007a). Although LANA does not seem to have any enzymatic activity for replication function, it is essential for TR-mediated replication primarily because it recruits the required cellular replication machinery to the RE element of the TR (Stedman *et al.*, 2004; Verma *et al.*, 2006). The primary replication protein, origin recognition complexes (ORCs), which serves as the launching pad for the recruitment of other proteins including MCMs gets recruited by LANA at the RE site of the TR (Verma *et al.*, 2006). Chromatin immunoprecipitation assay with hyper-acetylated histone H3 and H4 antibodies primarily detects the TR region suggesting a loose chromatin structure at the TR which is indicative of replicative origin (Stedman *et al.*, 2004). LANA-mediated TR replication as well as replications mediated by the autonomous elements was done on a plasmid-based assay. Therefore, we cannot conclusively state that these sites are firing during replication of the viral genome. A comprehensive study to demonstrate the usage of these replication sites would be important in understanding the mechanism of latent viral DNA replication.

KSHV-infected PEL cells maintain similar number of copies of the viral episome over multiple rounds of cell division suggesting a faithful mechanism of viral genome segregation after each cell division (Skalsky *et al.*, 2007). As discussed earlier, LANA associates with the KSHV genome in infected cells and colocalizes with the viral genome at inter-phase nuclei and on mitotic chromosome as a punctuate pattern (Ballestas *et al.*, 1999; Cotter and Robertson, 1999). The ability of LANA to tether viral episomes to the host chromatin is important for the establishment of latent infection. Studies with a KSHV genome deleted for LANA ORF cloned in a bacterial artificial chromosome showed loss of viral episomes from the infected cells without establishment of latency (Ye *et al.*, 2004). Another study where LANA expression was depleted using the shRNA strategy in PEL cells showed reduction of viral episomes to 20% compared to the control shRNA treated cells (Godfrey *et al.*, 2005). These studies clearly indicate that the presence of LANA in the host cells is required for persistence of the viral DNA. LANA binding to the host chromatin at nucleosomal surface through histones and other cellular proteins throughout the cell cycle confirms that the LANA: cellular proteins interactions are critical in maintaining the viral genome (Barbera *et al.*, 2006; Cotter and Robertson, 1999; Krithivas *et al.*, 2002; Lim *et al.*, 2003; Matsumura *et al.*, 2010; Si *et al.*, 2008; Verma *et al.*, 2007b; Viejo-Borbolla *et al.*, 2005; You *et al.*, 2006). A yeast-2-hybrid assay using the LANA-N terminus as bait identified the Nuclear Mitotic Apparatus (NuMA) protein as a LANA interacting protein (Si *et al.*, 2008). NuMA is an essential protein for cellular genome segregation, which interacts with a number of essential mitotic components including microtubule proteins dynein and dynactin during mitosis to efficiently segregate the daughter chromatids (Du *et al.*, 2002; Merdes *et al.*, 1996). Depletion of NuMA by siRNA and dominant-negative approach to block NuMA function has resulted in decreased copies of latently maintained KSHV episome (Si *et al.*, 2008). Proteomic analysis of LANA binding proteins from KSHV-infected cells identified a centromeric protein F, a component of multiprotein complex that assembles on centromeric DNA and links the chromosome to microtubule during mitosis

and associates with the kinetochore (Cheeseman *et al.*, 2005; Liao *et al.*, 1995). LANA associates with CENP-F and a kinetochore protein, Bub1 in KSHV-infected cells. Interestingly, depletion of Bub1 by shRNA dramatically reduced the number of latently persisting KSHV genomes (Xiao *et al.*, 2010). These studies suggest that KSHV episomal DNA segregates in a fashion similar to the case of the host genome at the same time usurping the cellular segregation mechanism.

B. Lytic replication

Lytic cycle is characterized by the expression of most of the viral genes in an orderly fashion (immediate early, early, and late) and the production of infectious virion particles. Gene expression profiles of KSHV have been studied in biopsies from KS tissue, PELs, and MCD, and also in *in vitro* setting by *de novo* infection of the cultured cells. These studies show that the majority of tumor cells in the KS biopsies contain KSHV viral DNA and express viral latent transcripts, and that a subpopulation (1–3%) of tumor cells undergo lytic reactivation as demonstrated by the expression of early and late viral transcripts (Staskus *et al.*, 1997; Sun *et al.*, 1999). These lytic transcripts include viral macrophage inflammatory protein-I, viral interleukin 6, viral Bcl-2 homolog, and polyadenylated nuclear RNA (PAN RNA). The subpopulation of cells undergoing lytic reactivation also express the late viral transcripts major capsid protein (MCP) and the small viral capsid (sVCA) which indicates production of virion particles and potentially go on to infect the surrounding cells. Additionally, the cells undergoing lytic reactivation produce cellular cytokines, which may create a favorable microenvironment to enhance the growth of latently infected cells and contribute to tumor progression. In order to study the full-blown lytic reactivation, PEL cells (BC-1, BC-3, and BCBL-1) can be treated with chemical agents such as phorbol esters or sodium butyrate (NaB) to induce the cascade of lytic cycle genes and the detection of viral transcripts shows immediate early, early, and late gene patterns like other herpesvirus (Gradoville *et al.*, 2000; Renne *et al.*, 1996b; Sarid *et al.*, 1998; Zhong *et al.*, 1996).

1. KSHV lytic genes—The lytic genes are classified into three major groups, immediate early (IE), early (E), and late (L) genes. The immediate early genes are the first group of genes expressed during lytic replication whose transcription generally does not require *de novo* protein synthesis. The immediate early genes encode for proteins with regulatory functions in activating cascade of downstream genes and also modulating the host cell environment for viral replication. PEL cells treated with TPA and NaB to activate lytic a cascade as well as primary cells, TIME, HFF, and 293 cells infected with the KSHV virus have identified a number of immediate early genes which include ORF50, ORF45, ORF K4.2 (Gradoville *et al.*, 2000; Krishnan *et al.*, 2004; Lukac *et al.*, 1999; Sarid *et al.*, 1998; Sharma-Walia *et al.*, 2005). ORF50, also called RTA is the best-characterized immediate early gene. RTA is 691aa long, which has an N-terminal DNA binding and dimerization domain, C-terminal activation domain, and two nuclear localization signals (Lukac *et al.*, 1998; Sun *et al.*, 1998). The molecular weight (110 kDa) of RTA is higher than the predicted (73.3 kDa) size because of various posttranslational modifications (Lukac *et al.*, 1999; Song *et al.*, 2002). Studies from various laboratories have shown that RTA serves as a molecular switch from latent to lytic cycle and ectopic expression of RTA into PEL cells induces the cascade of lytic gene expression including vIL-6, PAN RNA, ORF59, ORF65, and K8.1 and production of DNase-resistant encapsidated viral DNA, providing proof that RTA is capable of driving complete viral lytic cycle (Gradoville *et al.*, 2000; Lukac *et al.*, 1998; Sun *et al.*, 1998).

The expression of RTA is controlled by various cellular and viral proteins, including, RTA itself representing an important strategy used by KSHV to express sufficient amounts of RTA to activate the lytic cycle (Gradoville *et al.*, 2000; Lan *et al.*, 2004). RTA activates its

promoter by binding to the Oct-1 transcription factor and RBP-Jκ, a known cellular partner of RTA bound to the RTA promoter (Deng *et al.*, 2000; Liang *et al.*, 2002). Even though RTA has a DNA-binding domain, direct binding of RTA to its promoter is not required for it autoactivation as Oct-1–RTA complex was not detected in gel shift assay and a defective DNA-binding RTA mutant was capable of autoactivating through binding with RBPJκ (Chang *et al.*, 2005; Liang *et al.*, 2002; Sakakibara *et al.*, 2001). Latent protein, LANA also controls RTA expression and suppress lytic reactivation by repressing basal RTA promoter activity as well as RTA-mediated autoactivation (Lan *et al.*, 2004). LANA-mediated suppression of RTA promoter is dependent on RBP-Jk, which is also involved in RTA auto-activation suggests that LANA may be suppressing RTA autoactivation by competing with RTA for binding to RBP-Jk (Lan *et al.*, 2005). Since RBP-Jκ is one of the key molecules in both positive and negative regulation of RTA expression, the levels of LANA and RTA stringently controls the latent to lytic switch. Additionally, RTA upregulates LANA expression to suppress lytic reactivation and thus acts as a negative feedback regulator of RTA (Lan *et al.*, 2005; Matsumura *et al.*, 2005).

The early (E) genes generally encode proteins that are involved in nucleic acid metabolism, modulation of cellular functions, and their expression is controlled by the IE genes. RTA activates a number of early lytic genes by either direct or indirect mechanisms and they include PAN RNA, Kaposin, ORF57, K-bZIP (K8), vIL-6, K5, K9, K14, K15, ORF6, ORF59, ORF21, and ORF74 (Chang *et al.*, 2000; Chen *et al.*, 2000; Haque *et al.*, 2000; Jeong *et al.*, 2001; Lukac *et al.*, 2001; Wong and Damania, 2006; Zhang *et al.*, 1998).

Among the early gene transcripts, PAN RNA is most abundant transcript comprising approximately 80% of the total polyadenylated RNA in the infected cells. PAN RNA is a novel 1.1–1.2-kb noncoding polyadenylated transcript whose expression is controlled by RTA (Song *et al.*, 2001). The function of PAN RNA in lytic reactivation and pathogenesis is yet to be resolved. Kaposin, which is expressed during latent infection but strongly induced by lytic reactivation, has the ability to drive cell transformation (Kliche *et al.*, 2001; Muralidhar *et al.*, 1998). RTA controls the expression of Kaposin (E) through RRE (RTA response element) site within the Kaposin promoter (Song *et al.*, 2003). ORF57 encodes a post-transcriptional regulator, a conserved protein in herpesviruses, which is upregulated by RTA expression (Duan *et al.*, 2001; Kirshner *et al.*, 1999). ORF57 promotes the accumulation (stabilization) and export of viral intronless RNA transcripts by a mechanism, which is yet to be clearly defined. vMIP-1, a virus encoded chemokine homologue, is also expressed during early lytic cycle and its expression is controlled by RBP-Jκ and RTA protein–protein interaction and formation of a macromolecular complex at the RBP-Jκ binding site at the vMIP promoter (Chang *et al.*, 2005).

KSHV encodes vIL-6 (encoded by ORFK2) which is an early protein of lytic cycle. vIL-6 has 25% amino acid similarity with the human homologue (IL-6) and promotes growth and proliferation of IL-6-dependent human B cells similar to the human IL-6 (Moore *et al.*, 1996; Nicholas *et al.*, 1997). The immediate early gene, RTA strongly induces the expression of vIL-6 by binding to the RRE site making vIL-6 one of the most abundant transcripts in PEL cells during lytic reactivation (Deng *et al.*, 2002; Sun *et al.*, 1999). KSHV-encoded G protein-coupled receptor (vGPCR) is also an early gene which plays an important role in angiogenesis. vGPCR is expressed from a bicistronic RNA with K14 at the 5′ end and vGPCR at the 3′ end (Nador *et al.*, 2001). The promoter controlling K14/vGPCR is highly responsive to RTA, which binds to RBP-Jκ to upregulate the transcription of this K14/vGPCR transcript (Liang and Ganem, 2004). K-bZIP (K8), a basic leucine zipper protein, plays an important role in lytic viral DNA replication, and is an early protein whose expression is controlled by RTA (Lin *et al.*, 2003). RTA also controls the expression of

other early and late gene by either directly binding to the RTA response elements or through binding with other cellular factors (West and Wood, 2003).

2. KSHV reactivation—KSHV establishes lifelong latency with the persistence of viral genome as chromatin with the expression of only latency-associated genes. These genes maintain latency by blocking the expression of the immediate early gene. However, certain physiological conditions including hypoxia and pharmaceutical agents may trigger the expression of RTA (Cai *et al.*, 2006a; Chen *et al.*, 2001; Haque *et al.*, 2003). During latency, viral genomes are assembled into a nucleosomal structure with DNA wrapped around histones (Shinohara *et al.*, 2002; Stedman *et al.*, 2004). Tail modifications of histones play an important role in determining chromatin structure and condensation, both of which are important in regulating transcriptional activity. Acetylation of core histone tail by histone acetyltransferases (HATs) leads to the loosening of the chromatin and thus makes it transcriptionally active (Niedermeier *et al.*, 2006). In contrast, deacetylation of histone tails by histone deacetylases (HDACs) condenses the chromatin making it transcriptionally inactive (Lu *et al.*, 2003; Stedman *et al.*, 2004). HDACs associate with the RTA promoter during latency resulting in hypoacetylated histones and an inactive promoter (Lu *et al.*, 2003). Treatment of latently infected PEL cells with HDAC inhibitors, NaB, and TPA leads to hyperacetylation of histones with the recruitment of HATs and expression of RTA and other lytic genes (Lu *et al.*, 2003).

Methylation of DNA also plays an important role in controlling lytic reactivation as the inhibitor of DNA methyltransferases, 5-azacytidine (5-AzaC) stimulates KSHV lytic cycle (Chen *et al.*, 2001). KSHV genome does not seem to have extensive methylation but promoters of specific genes like RTA and LANA have been shown to be controlled by methylation (Chen *et al.*, 2001). BCBL-1 cells showed extensive methylation at the RTA promoter in latent cells and treatment with 5-AzaC results in demethylation of ORF50 promoter and expression of ORF50 and early (vIRF) and late gene (K8.1; Chen *et al.*, 2001).

As indicated above, chromatin remodeling due to histone modification can modulate transcriptional activity. The HAT inducer, TPA can induce lytic cycle by activating and enhancing the DNA-binding activity of transcription factors (Wang *et al.*, 2004c). TPA can induce the expression of C/EBPalpha transcription factor and enhance its transactivation activity. Since RTA promoter has C/EBPalpha binding site, expression is enhanced by TPA (Wang *et al.*, 2004c). TPA can also enhance the binding of the AP-1 transcription factor at the RTA promoter to induce RTA expression (Wang *et al.*, 2004c). A number of KSHV proteins including vIRF, LANA, RTA, and K-bZIP have been shown to interact with the transcriptional coactivators p300 and CBP (CREB-binding protein; Huang *et al.*, 2001; Lim *et al.*, 2001; Seo *et al.*, 2000). CBP/p300 has intrinsic HAT activity and RTA binding positively regulates HAT activity (Gwack *et al.*, 2001a). However, binding of LANA, vIRF, and K-bZIP leads to a reduction in protein's HAT activity (Hwang *et al.*, 2001; Lim *et al.*, 2001; Wang *et al.*, 2003). NaB-mediated activation of ORF50 transcription is due to the binding of the Sp1 transcription factor at the RTA promoter (Ye *et al.*, 2005). LANA regulates ORF50 activity by directly binding to ORF50 promoter and binds to Sp1 during latency (Lu *et al.*, 2006; Verma *et al.*, 2004). Treatment of PEL cells with NaB results in acetylation of LANA resulting in the disruption of LANA from ORF50 promoter bound to Sp1 (Lu *et al.*, 2006). Therefore, it can be speculated that removal of LANA from the ORF50 promoter and Sp1 may allow ORF50 and Sp1 to form a complex which enhances transcription.

Posttranslational modification including sumoylation, phosphorylation, and ADP-ribosylation of viral proteins, primarily RTA, plays an important role in viral reactivation. Poly(ADP-ribose) polymerase 1 (PARP-1) and a kinase, hKFC interacts with RTA to

ribosylate and phosphorylate which reduces the transcriptional activity of RTA by abolishing binding to RRE (Gwack *et al.*, 2003). Sumoylation of K-bZIP also plays a role in modulating k-bZIP-mediated RTA activation of KSHV-specific promoters (Izumiya *et al.*, 2005). These studies propose that posttranslation modifications of viral proteins are required to regulate KSHV lytic replication.

III. KSHV PRIMARY INFECTION

Studies for characterization of KSHV primary infection totally relies on the development of systems with high infection efficiency. KSHV produced from PEL and sometimes KS lesions has been showed to infect various cell types but with limited primary infection efficiency or failure of long-term infection. Based on all the systems examined so far, KSHV was found to eventually establish latency after primary infection (Fig. 2). However, depending on cell types or infection conditions, it has been shown that KSHV either enters latency immediately or starts the full productive replication phase followed by establishment of latency infection (Dezube *et al.*, 2002; Foglieni *et al.*, 2005; Gao *et al.*, 2003). Interestingly, the first description of KSHV primary infection system was tested in 293 cells (Foreman *et al.*, 1997). However, due to the direct involvement of endothelial cells in KS tumors, many groups have mainly focused on investigation of KSHV infection in human primary endothelial cells (Ciufo *et al.*, 2001; Flore *et al.*, 1998; Lagunoff *et al.*, 2002; Moses *et al.*, 1999). Initially, it was reported that KSHV infected only a small number of human primary endothelial cells *in vitro*, like bone marrow microvascular endothelial cells and human umbilical vein endothelial cells (HUVEC; Flore *et al.*, 1998). Subsequent study showed that KSHV was also able to infect primary human dermal microvascular endothelial cells (DMVEC; Moses *et al.*, 1999). The KSHV-infected cells present a typical KS spindle morphology and are able to survive for many months while the uninfected cells go to senescence within a few weeks of been in culture (Flore *et al.*, 1998). The efficiency of primary cell infection in these systems remains very low, although some studies are suggesting strategies for improvement. To further investigate whether the other genetic factors contribute to KSHV primary infection, several similar studies were performed in the E6/E7 or telomerase-immortalized DMVEC culture (Moses *et al.*, 1999). Surprisingly, KSHV infection in the telomerase-immortalized DMVEC shows that it is high. However, the growth of the virus in these cells is not sustained in long-term culture or reactivation to induce lytic replication (Moses *et al.*, 1999). Overall, the limitations in the systems mentioned above have restricted their use to be able to use them for further characterization of KSHV infection. Fortunately, in contrast to the systems above, the recombinant KSHV Bac36 is able to efficiently infect HUVEC cultures and produces large amounts of infectious virion as well as can establish latency at a later stage of infection (Gao *et al.*, 2003). The latently infected cells can be induced to lytic replication by TPA and NaB. This provides a possible path for examining KSHV latent and lytic replication via primary infection (Gao *et al.*, 2003).

A. KSHV entry and internalization

Similar to other herpesvirus, the process of KSHV primary infection includes two steps: attachment (or binding) and entry (Spear and Longnecker, 2003). The attachment allows viral proteins to contact with host cell coreceptors, and then stimulate the entry step by either a fusion event between envelope and cell membrane, or receptor-mediated endocytosis (Spear and Longnecker, 2003). KSHV encodes several transmembrane glycoproteins that are involved in attachment and entry into target cells. Some of them are conserved among the herpesvirus like gB (ORF8), gH (ORF22), gL (ORF47), gM (ORF39), and gN (ORF53; Koyano *et al.*, 2003; Krishnan *et al.*, 2005). Some are unique and share no significant homology with glycoproteins of other herpesvirus like K1, K8.1A, K8.1B, and vOX-2(K14) (see Table 2; Chandran *et al.*, 1998; Chung *et al.*, 2002; Li *et al.*, 1999; Luna *et*

al., 2004). KSHV was also shown to attach to the cell surface molecules heparin sulfate (Akula *et al.*, 2001a,b), integrin α3β1 (Akula *et al.*, 2002), and DC-SIGN (dendritic cell-specific ICAM-3-3-grabbing nonintegrin; Rappocciolo *et al.*, 2006).

After attachment, KSHV enters the target cell via fusion at the plasma membrane or via endocytosis. KSHV fuses with the plasma membrane to enter target cells as shown for 293 cells and MVDECs (Dezube *et al.*, 2002; Inoue *et al.*, 2003; Pertel, 2002). KSHV envelope proteins, gB, gH, gL, gM, gN, and gpK8.1A, are important and play key roles in the cell–cell fusion process (Chandran, 2010; Pertel, 2002). Endocytosis can occur through four major pathways which include clathrin-mediated endocytosis, caveolae, macropinocytosis, and novel nonclathrin, noncaveolae pathways (Kirchhausen, 2000; McPherson *et al.*, 2001; Sieczkarski and Whittaker, 2002). KSHV entry is via interactions with heparan sulfate (HS) followed by temporal interactions with integrins and xCT (CD98) molecules (Kaleeba and Berger, 2006), followed by formation of endocytic vesicles. A recent report showed that KSHV infection induces RhoA GTPase as well as rearrangements of microtubules and the actin cytoskeleton by clathrin-mediated endocytosis pathway in endothelial cells (Sharma-Walia *et al.*, 2004). Thus, the actin dynamics play a pivotal role in internalization and endosomal sorting/trafficking of KSHV and clathrin-mediated endocytosis in HUVEC cells (Greene and Gao, 2009). KSHV also utilizes the actin polymerization-dependent macropinocytic pathway that involves a Rob34 GTPase-dependent late endosome and low-pH environment to entry into HMVEC-d and HUVEC cells (Raghu *et al.*, 2009). KSHV virions are seen in large endocytic vesicles within 5 min of HMVEC-d and HFF cell infection and fusion of the virions envelope with endocytic vesicles (Akula *et al.*, 2003; Raghu *et al.*, 2009).

B. KSHV interaction with cellular signaling pathways

1. MAPK signaling—The activation of the MEK/ERK, JNK, and p38 mitogen-activated protein kinase (MAPK) pathways is pivotal at several stages during KSHV infection. Their activation immediately following infection enables successful establishment of KSHV infection (Pan *et al.*, 2006; Sharma-Walia *et al.*, 2005). Subsequently, MAPK pathways are activated during reactivation of latent infection (Ford *et al.*, 2006; Xie *et al.*, 2008; Yu *et al.*, 2007). LANA is a major activator of the serum response element and MAPK pathways via interactions with a mediator complex (Roupelieva *et al.*, 2010). Extracellular heat shock protein 90 localizes to the cells surface (csHsp90) and is a cofactor for MAPK activation and latent viral gene expression during *de novo* infection by KSHV (Qin *et al.*, 2010a). These studies suggest that KSHV may utilize MAPK pathways to regulate viral infection and switch from viral latency to lytic replication.

2. JAK–STAT signaling—Cytokine-mediated JAK–STAT signaling controls a number of important biological processes like immune response, cell growth, and differentiation. It has been shown that KSHV infection constitutively activates receptor-associated Janus tyrosine kinases (JAKs) and thereby results in the subsequent phosphorylation of signal transducers and activators of transcription (STATs). For instance, KSHV infection upregulates gp130 receptor expression and leads to constitutive phosphorylation of JAK2/STAT3 activation (Morris *et al.*, 2008; Punjabi *et al.*, 2007). Further studies have indicated that both LANA and vGPCR play a role in regulation of JAK2/STAT3 signaling to produce angiogenic factors (Burger *et al.*, 2005; Muromoto *et al.*, 2006). Recent studies showed that not only is the IL-6 induced by the Tat protein of HIV-1which is dependent on activated STAT3 signaling, but also that IL-4/STAT6 signaling contributes to KSHV lytic replication (Chen *et al.*, 2009; Zeng *et al.*, 2007). This is further confirmed by our findings that KSHV LANA plays a role in inhibition of IL-4-mediated STAT6 phosphorylation for maintenance of latency and response to apoptosis stress (Cai *et al.*, 2010a).

3. Notch signaling—KSHV infection is essential for the development of Kaposi sarcoma (KS). Notch signaling is also known to play a pivotal role in KS cell survival and entry of KSHV into the lytic phase. KSHV-encoded RTA binds to RBP-Jκ and is a major end point of the Notch signal transduction pathway (Liang *et al.*, 2002; Persson and Wilson, 2010). Moreover, the KSHV-encoded LANA protein can stabilize activated forms of the Notch receptor by targeting the Sel10 protein (Lan *et al.*, 2007). KSHV also manipulates the Notch signaling pathway by directly increasing the expression of two Notch ligands (JAG1 and DLL4) through two KSHV genes expressed during latent and lytic infection, respectively (Emuss *et al.*, 2009). These results showed that KSHV infection can manipulate the Notch signaling pathway to influence cell proliferation and differentiation.

4. HIF signaling—Hypoxia-inducible factor (HIF) is a ubiquitously expressed transcriptional regulator that involves an induction of numerous genes associated with angiogenesis and tumor growth. HIF is a heterodimer which composes of inducible α subunit and a constitutively expressed β subunit. It has been demonstrated that there are at least three isoforms of HIFα (HIF1α, HIF2α, and HIF3α) in human cells. In the presence of oxygen, HIFα is hydroxylated and ubiquitylated for proteasomal degradation (Maxwell *et al.*, 1999; Ravi *et al.*, 2000). However, under hypoxic conditions, HIFα hydroxylation is blocked and become stable to activate large number of downstream genes associated with angiogenesis, erythropoiesis, and glycolysis (Lee *et al.*, 2004; Seagroves *et al.*, 2001). Due to the powerful activation of HIF signaling, it has been demonstrated that HIFα is aberrantly overexpressed in many cancers and there is a striking correlation with tumor grade and vascularization (Zagzag *et al.*, 2000; Zhong *et al.*, 1999). In the KSHV-associated cancers, we and other groups have found that HIF1α and HIF2α are overexpressed in KSHV latently infected cells and tissues (Cai *et al.*, 2007; Carroll *et al.*, 2006). Furthermore, both latent antigens LANA and vIRF3 play a role on the HIF1 α stabilization via protein–protein interaction (Cai *et al.*, 2006b, 2007; Shin *et al.*, 2008). Recent analysis of clinical patient samples further supported a role for LANA in stabilization of HIF1α (Long *et al.*, 2009). Interestingly, the lytic antigen vGPCR has also been shown to upregulate VEGF expression through activation of HIF1α expression (Sodhi *et al.*, 2000). These results suggest that HIF1α is stringently targeted by KSHV during both latent and lytic replication.

5. Wnt signaling—KSHV uses components of Wnt pathways to regulate their own viral gene expression and additionally alter cell gene expression through mimicry or manipulation of downstream pathway responses after entry the cells. LANA stabilizes β-catenin by interacting with GSK-3β and inducing its nuclear translocation, thereby preventing phosphorylation of β-catenin in the cytoplasm and stimulation of TCF/LEF-dependent transcription (Fujimuro and Hayward, 2003, 2004). And the I-mfa domain proteins, HIC (human I-mfa domain-containing protein), and I-mfa (inhibitor of MyoD family) interact with LANA and negatively regulate LANA-mediated activation of Wnt signaling-dependent transcription (Kusano and Eizuru, 2010). These data suggest that LANA-mediated dysregulation of β-catenin can play an important role in KSHV-mediated transformation after primary infection.

6. miRNA—Like all herpesviruses, KSHV has a large, double-stranded DNA genome (~160 kb; Russo *et al.*, 1996). KSHV encodes more than 85 protein-coding genes, and at least 12 pre-miRNAs that give rise to at least 17 different miRNAs (16 different 5p or 3p miRNAs, and a single-nucleotide-edited miRNA) that are highly conserved (Lin *et al.*, 2010; Marshall *et al.*, 2007). These viral miRNAs interact with cellular factors important for establishment and/or maintenance of KSHV latent infection. For instance, miR-K12-11 upregulates xCT expression in both KSHV-infected macrophages and endothelial cells via suppression of BACH-1 (Qin *et al.*, 2010b). miR-132 regulates the innate antiviral immunity

by inhibiting expression of the p300 transcriptional coactivator (Lagos *et al.*, 2010). KSHV-encoded viral FLICE inhibitory protein vFLIP suppresses CXCR4 expression by upregulating miR-146a (Punj *et al.*, 2010). KSHV-encoded miRNAs target the leucine zipper transcription factor MAF (musculoaponeurotic fibrosarcoma oncogene homolog) and downregulates its expression during primary KSHV infection (Hansen *et al.*, 2010). MicroRNA miR-K1 inhibits p21 expression and attenuates p21-mediated cell-cycle arrest (Gottwein and Cullen, 2010). miR-K1 also regulates NF-κB inhibitor IκBα and viral replication by targeting the 3′UTR of its transcript (Lei *et al.*, 2010), and KSHV miRNA cluster can derepress the ORF50 (RTA) transcription (Lu *et al.*, 2010). These studies suggest that viral miRNAs play a critical role in establishment and/or maintenance of KSHV latent infection.

C. Animal and virus models

To date, many animal and virus models have been developed to investigate the *in vivo* behavior of KSHV-related malignancies. For animal models, BCBL-1 and infected PEL cells were injected alone or with human peripheral blood mononuclear cells (PBMCs) into SCID mice (Boshoff *et al.*, 1998; Picchio *et al.*, 1997). SCID-Hu Thy/Liv mice were utilized to study viral transcription as well as the susceptibility of the mice to infection with BCBL-1-derived KSHV (Dittmer *et al.*, 1999; Parsons *et al.*, 2006). Similarly, injection of KSHV in human skin engrafted on SCID mice induces KS-like lesions (Foreman *et al.*, 2001). FVB/N transgenic mouse lines that express constitutively active Rac1 (V12 mutant or RacCA) under the control of the α-smooth muscle actin (α-SMA) promoter can develop tumors resembling KS (Ma *et al.*, 2009). Recently, one study reported the successful zoonotic transmission of KSHV into common marmosets (*Callithrix jacchus*, Cj), a New World primate. Marmosets infected with the recombinant KSHV rapidly seroconvert and maintain a vigorous anti-KSHV antibody response. KSHV DNA and LANA were readily detected in the PBMCs and tissues of the infected marmosets (Chang *et al.*, 2009). Recently, Lossos group developed a direct xenograft model, UM-PEL-1, by transferring freshly isolated human PEL cells into the peritoneal cavities of NOD/SCID mice without *in vitro* cell growth to avoid the changes in KSHV gene expression evident in cultured cells, showing that bortezomib induces PEL remission and extends overall survival of mice bearing lymphomatous effusions (Sarosiek *et al.*, 2010).

For virus models, rhesus monkey rhadinovirus (RRV) infection results in the development of abnormal cellular proliferations and can coinfect rhesus macaques with simian immunodeficiency virus. This has been suggested as an excellent primate model to investigate KSHV-like pathogenesis (Orzechowska *et al.*, 2008; Wong *et al.*, 1999). Another homolog of KSHV—retroperitoneal fibromatosis-associated herpesviruses (RFHV), is its ability to develop a malignancy closely resembling KS and retroperitoneal fibromatosis in animal that become immunodeficient after infection with a simian virus (Bruce *et al.*, 2006).

Murine gammaherpesvirus 68 (MHV-68) is a small mouse model, but its infection is not associated with KS-like and related diseases (Flach *et al.*, 2009; Virgin *et al.*, 1997). Herpesvirus saimiri (HVS) mainly infects New World primates and results in T-lymphoproliferative disorder (Jung *et al.*, 1999). Additionally, two types of cell lines carrying KSHV are able to generate KSHV-associated tumors. One is based on HUVECs that express telomerase (TIVE-LTC; An *et al.*, 2006; Sadagopan *et al.*, 2009), and the other is based on normal mouse bone marrow endothelial lineage cells (Meck36) transfected with the KSHV-infectious bacterial artificial chromosome (KSHV-Bac36; An *et al.*, 2006; Mutlu *et al.*, 2007).

IV. KSHV-MEDIATED ONCOGENESIS

Due to the extensive association of KSHV with two different human malignancies (KS and PEL), KSHV is considered to be a human oncogenic virus (Brooks *et al.*, 1997; Cathomas, 2003; Ensoli and Sirianni, 1998). Unlike other oncogenic viruses, KSHV is a complex DNA virus and infection not only leads to cell (endothelial) morphology changes, growth rate, and extended life span, but also provokes deregulated angiogenesis, inflammation, and modulation of immune system in favor of tumor growth (Fig. 3; Dagna *et al.*, 2005; Ensoli and Sturzl, 1998). However, in most experimental systems *in vitro* infection of endothelial cells with KSHV did not fully result in neoplastic transformation. Moreover, although KSHV encodes oncogenic genes that could potentially induce all KS-related malignant phenotype, the evidences which link KSHV infection to the development of KS mostly occurs in AIDS or immunosuppressed patients, but rarely in general population. This indicates that the presence of KSHV DNA alone in healthy individuals is not sufficient to cause clinical KS, and that the existence of cofactors like HIV infection or drug-induced immunosuppression are important for KSHV-associated disease progression (Cathomas, 2003; Goedert, 2000).

In view of the fact that the vast majority of KS spindle cells are latently infected with KSHV, it has been documented that latent infection plays an essential role in KSHV-induced malignancy and pathogenesis (Deng *et al.*, 2004; Fakhari *et al.*, 2006; Staudt and Dittmer, 2003). Nevertheless, a small percentage of infected cells were also found to undergo lytic replication leading to production of mature virus and cell lysis. This indicates that KSHV lytic replication may also be important for KS development (Fig. 3). This notion is further supported by the facts that some drugs targeting KSHV replication have been shown to be effective in inhibiting KS tumor growth *in vivo* (Mocroft *et al.*, 1996; Robles *et al.*, 1999), and that there was a strong correlation between viral load and progression of KS tumor (Brown *et al.*, 2005; Duprez *et al.*, 2005; Polstra *et al.*, 2004).

A. Induction of cellular growth and survival

Extensive studies have shown that KSHV targets multiple pathways to induce cell proliferation and survival for promoting tumor development. One line of evidence is that genetic instability is found to be commonly seen in KS tumors and PEL cells (Delli Bovi *et al.*, 1986; Gaidano *et al.*, 1997; Popescu *et al.*, 1996), and that KSHV infection is sufficient to induce chromosome instability (Pan *et al.*, 2004). This requires at least five KSHV genes —LANA-1 (or LANA; Cai *et al.*, 2006b; Friborg *et al.*, 1999; Radkov *et al.*, 2000; Si and Robertson, 2006), RTA (Gwack *et al.*, 2001b), k-ZIP, LANA-2 (Rivas *et al.*, 2001), and vIRF-1 (Nakamura *et al.*, 2001; Seo *et al.*, 2001; Shin *et al.*, 2006), which have been shown to interact with and suppress the function of tumor suppressor p53 and Rb resulting in suppression of their activities. Loss of p53 and Rb function leads to inhibition of the DNA damage repair, cell death, and cell-cycle checkpoint which contribute to KSHV-induced oncogenesis. Furthermore, to accelerate cellular proliferation, KSHV encodes vCyclin to promote cell-cycle progression from G1 to S phase by interaction with phosphorylated cyclin-dependent kinase 6 (Cdk6; Chang *et al.*, 1996; Child and Mann, 2001; Godden-Kent *et al.*, 1997; Li *et al.*, 1997; Sarek *et al.*, 2006).

Due to constant selection pressure of favoring cell survival, viruses have evolved different strategies to avoid apoptosis to promote tumor growth and survival by dysregulating cellular signaling pathways. For instance, KSHV encodes vFLIP (K13/ORF71), which like its cellular homolog FLIP, contains the DED domain to inhibit apoptosis by blocking signaling through the death receptor (Belanger *et al.*, 2001; Djerbi *et al.*, 1999). Nevertheless, a recent report utilizing a transgenic mouse model questions the ability of vFLIP to inhibit Fas-mediated apoptosis (Chugh *et al.*, 2005). Several studies have suggested that the

antiapoptosis ability of vFLIP is primarily associated with the activation of NF-kB pathway which is essential for cell survival (Chaudhary *et al.*, 1999; Field *et al.*, 2003; Guasparri *et al.*, 2006; Keller *et al.*, 2000, 2006; Liu *et al.*, 2002; Matta and Chaudhary, 2004; Matta *et al.*, 2003;Sun *et al.*, 2005, 2006). Consistently, NF-kB activation by vFLIP leads to cellular transformation and an increased incidence of lymphoma in the transgenic vFLIP mice (Chugh *et al.*, 2005; Sun *et al.*, 2003). It is also important to note that KSHV constitutively activates the NF-kB pathway by encoding vGPCR to produce several cytokines and chemokines (Bais *et al.*, 1998; Couty *et al.*, 2001, 2009; Grisotto *et al.*, 2006; Montaner *et al.*, 2001; Munshi *et al.*, 1999; Schwarz and Murphy, 2001) and vIRF1–3 (Burysek *et al.*, 1999;Flowers *et al.*, 1998; Gao *et al.*, 1997; Kirchhoff *et al.*, 2002; Li *et al.*, 1998; Lubyova and Pitha, 2000; Seo *et al.*, 2002). Treatment with inhibitors of the NF-kB pathway has been shown to completely repress PEL tumors in a mouse model and *in vitro* tissue culture (Keller *et al.*, 2006; Wang and Damania, 2008). In addition, KSHV was found to promote cell proliferation through autocrine and/or paracrine signaling by encoding or inducing the secretion of various growth factors such as vIL-6 (Molden *et al.*, 1997; Nicholas *et al.*, 1997), IL-6 (Xie *et al.*, 2005), IL-8 (Cerimele *et al.*, 2001), VEGF (Masood *et al.*, 2002), and basic fibroblast growth factor (bFGF; Naranatt *et al.*, 2004; Wang *et al.*, 2004a). It is believed that a variety of cellular growth factors and cytokines regulated by KSHV all play pivotal roles in the development and progression of KS. In addition, cell death is shown to be deregulated by KSHV-encoded antiapoptotic proteins. For instance, KSHV-encoded cellular Bcl-2 homolog vBcl-2 (ORF16) is able to protect cells from Bax-mediated apoptosis (Cheng *et al.*, 1997; Polster *et al.*, 2004; Sarid *et al.*, 1997), and the viral homolog of human survivin also referred to as inhibitor of apoptosis protein (vIAP) encoded by KSHV ORF K7 was shown to inhibit caspase 3 activity and apoptosis by forming a bridge between cellular Bcl-2 and active caspase 3 (Mahotka *et al.*, 1999; Wang *et al.*, 2002).

Another critical strategy is that KSHV encodes a large nuclear antigen called LANA (ORF73), which has no cellular homologs. It has been documented that LANA is essential for many viral functions including gene expression, DNA replication, and episomal maintenance of KSHV genome (Ballestas *et al.*, 1999; Barbera *et al.*, 2006; Cotter and Robertson, 1999; Garber *et al.*, 2002; Hu *et al.*, 2002; Lim *et al.*, 2002). In addition to tethering the KSHV DNA to host chromosome during mitosis, LANA not only plays a role in the maintenance of latency by repressing the transcriptional activity of RTA (a lytic reactivator of KSHV; Lan *et al.*, 2004), but also induce oncogenesis by disrupting p53 and Rb function on cell-cycle checkpoint (Cai *et al.*, 2006b; Friborg *et al.*, 1999; Radkov *et al.*, 2000; Si and Robertson, 2006). Our recent studies suggested that LANA is also able to directly induce the level of cellular IAP expression to enhance the life span and proliferation of KSHV-infected cells (Lu *et al.*, 2009).

B. Regulation of angiogenesis

The typical tumor cell in KS biopsies is a spindle-shaped cell expressing endothelial cell markers with some markers for smooth muscle cells, macrophages, and dentric cells (Flore, 2004). Recent findings have shown that KS is a highly angiogenic neoplasm with dense and irregular shaped blood vessels, and that KSHV infection is involved in angiogenesis and lymphangiogenesis (Carroll *et al.*, 2004; Hong *et al.*, 2004; Wang *et al.*, 2004a). However, different from the angiogenesis in wound healing and female reproduction, pathological angiogenesis is correlated with tumor growth and metastasis (Carmeliet, 2005; Folkman, 2006). Although the mechanisms of angiogenesis in KS tumor development remain to be further elucidated, it has been demonstrated that KSHV-induced angiogenic factors and inflammatory cytokines play essential roles in driving the late stages of KS tumor development. For example, in an SCID mouse model with human skin grafts, neutralization of VEGF blocks the early-stage KS cells growing into KS-like tumors (Masood *et al.*, 2002;

Samaniego *et al.*, 2002). Many other angiogenic cytokines including bFGF, IL-6, IL-8, TNF-β, and ephrin B2 have also been shown to be targeted by KSHV (Masood *et al.*, 2005; Naranatt *et al.*, 2004; Wang *et al.*, 2004a; Xie *et al.*, 2005). In clinical samples, higher levels of serum VEGF and mRNA levels of angiopoietins (Ang-1 and Ang-2) were also seen in the AIDS patients with KS than without KS (Brown *et al.*, 2000; Weindel *et al.*, 1992). Moreover, cyclooxygenase-2 (Cox-2) and heme oxygenase-1 induced by KSHV infection were also shown to play an important role in angiogenesis (McAllister *et al.*, 2004; Sharma-Walia *et al.*, 2006, 2010a,b). In addition to the host factor, a number of KSHV-encoded proteins like vIL-6, vGPCR, vCCL-1, and vCCL-II has been shown to act in concert with vCyclin, vFLIP, and vIRF1 to stimulate hematopoiesis and promote angiogenesis by regulating the paracine secretion of angiogenesis-related growth factors and proinflammatory molecules through different signaling pathways (Aoki *et al.*, 1999; Lagos *et al.*, 2007; Montaner *et al.*, 2001, 2003, 2006; Sodhi *et al.*, 2000; Stine *et al.*, 2000). Moreover, recent studies have identified the small GTP-binding protein Rac1 as a key mediator of vGPCR-mediated paracine neoplasia. Prevention of the vGPCR-induced activation of Rac1 efficiently blocks the activation of a series of key transcription factors including NF-kB, AP-1, and NF-AT, and inhibition of cytokine secretion and sarcomagenesis *in vitro* and *in vivo* (Montaner *et al.*, 2004).

C. Immune evasion

It has been demonstrated that the immune evasion strategies exploited by KSHV leads to uncontrolled cell proliferation and thereby promote tumorigenesis (Choi *et al.*, 2001; Moore and Chang, 2003; Ploegh, 1998). With the exception of modulation of immune response, KSHV encodes multiple viral encoded proteins which are directly involved in the inhibition of host innate and adaptive immunity (Choi *et al.*, 2001; Means *et al.*, 2002). These include the viral proteins that interfere with interferon signaling, complement system, cytokine secretion, and antigen processing and presentation (Fig. 3).

1. Interference of interferon signaling—Interferon response is the first line of host immune response against viral infection (Fenner *et al.*, 2006). Host cells start to produce and secrete interferon α/β upon virus infection. It has been shown that the interferon response is regulated by cellular interferon factors (cIRFs) at the transcriptional level. To interfere with this response, KSHV encodes four viral homologs of IRF (vIRF1–4; Means *et al.*, 2002; Moore and Chang, 2003). Among these, vIRF1 functions as a repressor of cellular IFN-mediated signal transduction by directly binding to the IFN-stimulated response DNA element. Sequestration of p300/CBP provides another strategy for vIRF1 to broadly inhibit IFN-mediated gene expression (Li *et al.*, 2000). The observation of vIRF1-induced cell transformation and tumorigenesis in nude mice, suggests that vIRF1 plays a potential role in oncogenesis (Gao *et al.*, 1997; Li *et al.*, 1998). Another IRF encoded by KSHV is vIRF3 also called LANA-2 (Esteban *et al.*, 2003; Rivas *et al.*, 2001). It has been demonstrated that vIRF3 is a B cell-specific viral latent protein without DNA-binding ability and is able to inhibit dsRNA-activated protein PKR and p53-dependent apoptosis (Esteban *et al.*, 2003; Rivas *et al.*, 2001). Another mechanism for KSHV to evade the effect of interferon response is expressing viral IL-6. By using the different binding receptor from the cellular homolog, vIL-6 directly binds gp130 independent of gp80, and activates STAT1 phosphorylation and MAPK serine/threonine kinase pathways (Chatterjee *et al.*, 2002; Miles *et al.*, 1990; Molden *et al.*, 1997).

2. Dysregulation of complement system—Another strategy in the first defense mechanism against virus attack is to deregulate the complement system. Like many other viruses, KSHV also interferes with complement and this is targeted by the KSHV-encoded ORF4 also called complement control protein (KCP) which has homology to human

complement regulators (Mark *et al.*, 2004, 2006). Through four conserved element termed short consensus repeats (SCRs), KCP disrupts the progression of the complement cascade (Mark *et al.*, 2004, 2007; Mullick *et al.*, 2003; Spiller *et al.*, 2003, 2006). The disruption of complement activation in a mouse model can lead to both acute viral infection and establishment of latency has elucidated the importance of complement inhibition during virus infection (Kapadia *et al.*, 2002).

3. Viral induction of cytokine secretion—Cytokines are the signaling molecules that are used extensively in cellular communication for immune response. Normally, cytokines are unstable and short-lived, and this property is used to prevent too strong and detrimental a response from the host defense system. To promote cytokine stabilization, KSHV expresses the latent protein Kaposin B which activates the p38-MK2 pathway, and leads to increased expression of cytokines including cellular IL-6 and granulocyte-macrophage colony-stimulating factor (GM-CSF; McCormick and Ganem, 2005, 2006; Wang *et al.*, 2004a). Another strategy of KSHV modulation of cytokine signaling is by directly expressing signaling ligands and receptors. For instance, the transmembrane receptor KIS encoded by KSHV K1 gene is constitutively activated through its cytoplasmic immunoreceptor tyrosine-based activation motif (IATM; Lagunoff *et al.*, 1999; Lee *et al.*, 1998a). Upon stimulation, K1 IATM is tyrosine phosphorylated. The K1 signaling activates the PI3K/Akt pathway and in turn a series of downstream cellular transcription factors including AP-1, NF-AT, and NF-kB which lead to expression of a number of inflammatory cytokines, such as IL-6, IL-8, IL-10, and VEGF (Lee *et al.*, 1998b; Samaniego *et al.*, 2001; Wang *et al.*, 2004b). Further studies have confirmed that the K1 protein is an oncogenic protein which is able to transform primary HUVEC (Lee *et al.*, 1998b; Wang and Damania, 2008; Wang *et al.*, 2006). Besides Kaposin B and KIS, the latent protein vFLIP has also been shown to induce IL-8 and IL-6 expression via NF-kB and JNK/AP-1 pathways (An *et al.*, 2003; Sun *et al.*, 2006). Taken together, in the latently infected cells, KSHV-induced cytokine secretion can function in both autocrine and paracrine fashion, and may contribute to the development of KSHV-associated neoplasms.

4. Viral disruption of antigen processing and presentation—Antigen processing and presentation through the major histocompatibility complex (MHC) is a critical step in initiating effective cell-mediated adaptive immune response against pathogens. Downregulation of the cell surface MHC class I molecules is a key viral immune evasion strategy. KSHV encodes two zinc finger membrane proteins MIR1 and MIR2 (also called K3 and K5) which are E3 ubiquitin ligases for modulation by ubiquitylation of MHC I molecules on the infected cell surfaces (Coscoy and Ganem, 2000, 2001). The ubiquitylated MHC I molecules then undergoes endocytosis and is degraded in the lysosome (Coscoy *et al.*, 2001). Interestingly, it has also been demonstrated that MIR1 is able to act as an E3 ubiquitin ligase on ubiquitylation of lysineless molecules (Cadwell and Coscoy, 2005, 2008; Coscoy and Ganem, 2003). Additionally, MIR2 dow-regulates ICAM-1 and B7-2 which are ligands for NK cell-mediated cytotoxicity receptors (Ishido *et al.*, 2000). The second strategy for KSHV to evade the adaptive immune system is bu encoding several viral chemokines (vCCL). At least three vCCLs have been identified and known to inhibit Th1 cell-mediated immune responses by binding with cellular chemokine receptors on Th1 helper cells which result in blocking signal transduction of G-proteins (Means *et al.*, 2002; Moore and Chang, 2003). Additionally, KSHV also encodes its own versions of the chemokine receptors like vGPCR (Sodhi *et al.*, 2004a). vGPCR is a relative of cellular IL-8 receptors CXCR1 and CXCR2 (Sodhi *et al.*, 2004a). Similar to K1, vGPCR is also constitutively active and induces an array of proinflammatory cytokines and growth factors such as IL-1β, IL-6, IL-8, TNF-α, VEGF, and bFGF through AP-1, NF-kB, and HIF1 pathways (Montaner *et al.*, 2004; Schwarz and Murphy, 2001; Sodhi *et al.*, 2000). However,

vGPCR activates several downstream kinases including Lyn, JNK, Akt, and p38 not only by constitutive activation but also by certain induction of chemokines like IL-8 (Montaner *et al.*, 2001; Sodhi *et al.*, 2000, 2004b).

D. Response to microenvironmental stress

As the tumor progresses, the cancer cells and its surrounding tissues form a microenvironment with characterizations of both hypoxia and oxidative. Many observations have showed that premalignant cells progress differently in different microenvironments, and hinder the effectiveness of antitumor treatments such as radiation therapy and chemotherapy (Bissell and Radisky, 2001; Liotta and Kohn, 2001). This hostile microenvironmental stress not only promotes tumor growth and protects it from immune attack, but also affect the host's susceptibility to pathogens (Bissell and Radisky, 2001; Liotta and Kohn, 2001). KSHV-associated KS lesions are usually found in the lower extremity of the human body like the feet and hands where there is lower oxygen supply (hypoxia). Investigation of the relationship between the host microenvironment and viral tumor cells will provide new insights into the mechanisms of tumorigen-esis and will be a great value in development of therapeutic strategies against clinically relevant viral diseases (Fig. 4).

1. Hypoxia stress—The rapid progression of the primary tumor usually generates a hypoxic microenvironment inside the tumor lesion. To investigate the effect of hypoxic stress on KSHV-infected cells, we and others have demonstrated that KSHV is able to mimic hypoxic stress to establish latent infection in these cells (Cai *et al.*, 2007; Carroll *et al.*, 2006). Our studies further showed that the EC5S (Elongin BC-Cul5-SOSC-box) E3 ubiquitin complex is recruited by KSHV latent antigen LANA to degrade the HIF1α negative regulators p53 and VHL (Cai *et al.*, 2006b, 2007). A recent study also indicated that another latent antigen vIRF3 can play a role in stabilization of HIF1α and production of VEGF (Shin *et al.*, 2008). Interestingly, several studies have focused on the life cycle of KSHV and discovered that the KSHV genome contains multiple HIF1α-binding DNA elements, and that hypoxic stress induces KSHV lytic replication (Cai *et al.*, 2006a; Davis *et al.*, 2001; Haque *et al.*, 2003, 2006). In addition, hypoxia was also shown to increase the cell toxicity of ganciclovir and azidothymidine in PEL cells *in vitro* (Davis *et al.*, 2007; Long *et al.*, 2009), as well as inactivate the function of tumor suppressor VHL and so contribute to viral infection (Cai *et al.*, 2010b).

2. Oxidative stress—Oxidative stress represents an imbalance between the production of reactive oxygen species (ROS) and the cellular ability to remove ROS and repair cellular damage. When the concentrations of ROS exceed the ability of the cell to turn over these species, oxidative stress will result and lead to the widespread oxidation and damage of biomolecules including DNA and proteins (Berlett and Stadtman, 1997; Finkel and Holbrook, 2000). There is accumulating evidence which shows that oxidative stress can affect the interaction between the host and viral pathogens, and hence viral pathogenesis (Beck *et al.*, 2000). Recent studies have indicated that herpesvirus infections like HSV-1 and RRV can induce oxidative stress in cells and in tissues through induction of oxidized proteins which are enriched in the VICE (*v*irus-*i*nduced *c*haperone *e*nriched domains) foci in the nucleus (Mathew *et al.*, 2010). However, the biological consequences of virus-induced oxidative stress have not been fully characterized. For KSHV, it is speculated that the redox status may affect replication and pathogenicity of KSHV (Wang *et al.*, 2004d). Most recently, in transgenic Rac1 mice, it has been showed that constitutive activation of Rac1 is sufficient to cause KS-like tumors, and the treatment of antioxidants contributes to inhibition of KS-like tumor growth (Ma *et al.*, 2009). Additionally, it has been reported that KSHV-encoded miRNA upregulates xCT (the inducible subunit of a membrane-bound amino acid transporter) which facilitates KSHV dissemination and persistence in the environment of

oxidative stress (Qin *et al.*, 2010b). This indicates that oxidative stress can play a causal role in carcinogenesis mediated by chronic viral infection and inflammation and might be a potential target for therapeutic interventions.

V. POTENTIAL THERAPIES AGAINST KSHV-ASSOCIATED MALIGNANCES

Since the discovery of the virus, understanding of the molecular biology, pathogenesis, and tumorigenesis of KSHV have been increasing and lead to the development of rational therapeutic trials and drug design (Dittmer and Krown, 2007). Although the introduction of HAART (Highly active antiretroviral therapy) has effectively reduced the incidence of AIDS-KS in the USA (Nguyen *et al.*, 2008), it still remains a clinical problem with only half of patients achieving resolution (Vanni *et al.*, 2006). In addition to HAART, the current treatment regiments include radiotherapy and conventional chemotherapy (like liposomal daunorubicin and taxanes) are used to treat the symptoms (Vanni *et al.*, 2006). However, these therapies do not prevent new KS lesions from developing (Sullivan *et al.*, 2006, 2009). Several promising approaches are ongoing with preclinical or clinical trials. These aim to interrupt the angiogenesis process (VEGF/VEGFR, NF-kB/vFLIP, angiopoietin-2, DLL4, and MMP), cell proliferation (cKit/PDGFR, PI3K/AKT/mTOR, and Notch), or both (Rac/Ros; see reviewed elsewhere Dezube *et al.*, 2006; Dittmer and Krown, 2007; Mesri *et al.*, 2010; Sullivan *et al.*, 2006). Moreover, through targeting KSHV lytic replication, interferon-α is now used as an approved treatment for KS (Grundhoff and Ganem, 2004). Using lentivirus-mediated RNA interference to inhibit viral latent gene expression, has provided another feasible approach for treatment of established lymphomas in murine model (Godfrey *et al.*, 2005). Along with the discovery of the unique mechanisms used by viral pathogen, we believe that the use of antiviral agents and small molecules that specifically target the signaling pathways of KSHV-infected tumor cells will be effective therapies with fewer side effects in the treatment of KSHV-associated malignancies.

Acknowledgments

Due to space restrictions, we regret that we had to omit many important references. The work in authors' laboratory is support from the National Cancer Institute, including NCI CA072510 and CA091792, NIDCR DE014136, NIAID AI067037, and DE17338 (E. S. R.). E. S. R. is a scholar of the Leukemia and Lymphoma Society of America. S. C. V. is supported by the NIH pathways to independence award, CA126182.

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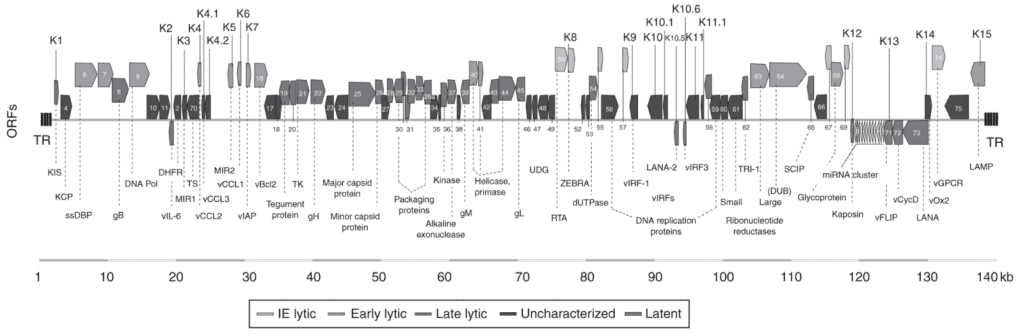

FIGURE 1.

A schematic of the KSHV genome consisting of 145 kb long unique, gene-coding region flanked with terminal repeat units. The coding regions contain over 90 open reading frames (ORFs; Russo *et al.*, 1996). The gene-encoded proteins are labeled in the bottom from left to right. ORFs unique to the KSHV are given the prefix K. The miRNA cluster encoding for 12 microRNAs (yellow) is located between K12 (Kaposin) and ORF71 (vFLIP). The blocks representing the ORFs are also labeled in color according to gene class [latent, immediate early (IE), early and late lytic, and unclassified] (based on previous reviews of Coscoy, 2007; Moore and Chang, 2001). (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this chapter.)

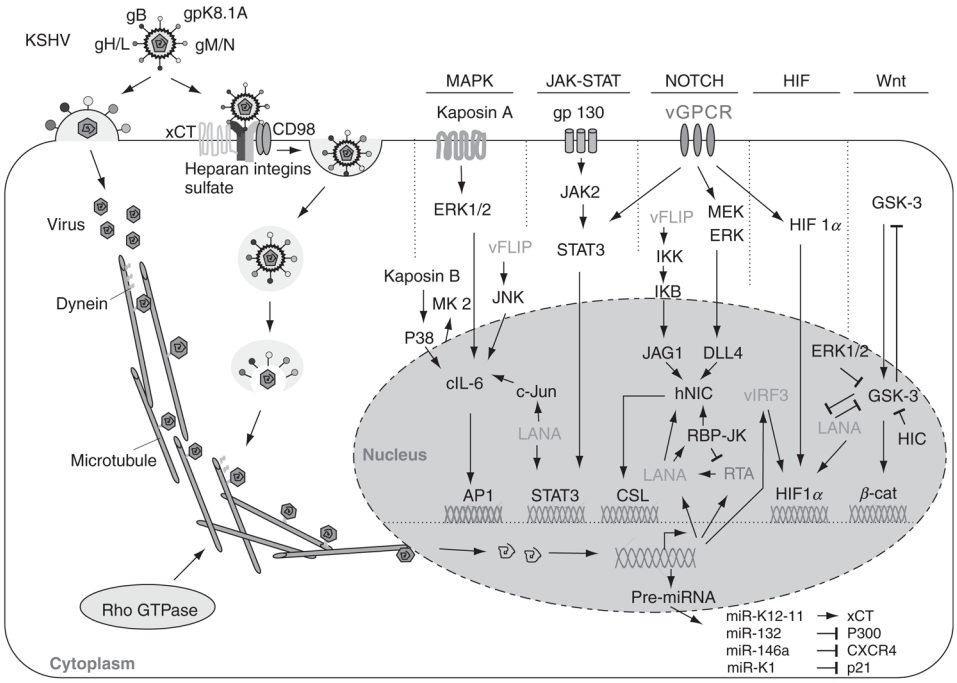

FIGURE 2.

KSHV primary infection and the cell signaling pathways targeted. Infection is initiated by cell fusion or endocytosis. For cell fusion, KSHV fuses with the plasma membrane by gB, gH, gL, gM, gN, and gpK8.1A, then release of virus particles to the cell plasma. For endocytosis, KSHV binds to the cell surface via interactions with heparan sulfate (HS) followed by temporal interactions with integrins and xCT (CD98) molecules, then formation of endocytic vesicles, virus entry, movement in the cytoplasm, release of virus particles, delivery into the nucleus by dynein along the microtubule. Viral gene expression interferes with the cellular signaling pathways such as MAPK, JAK–STAT, Notch, HIF, Wnt, and miRNA, consequently reprograms host cell gene expression.

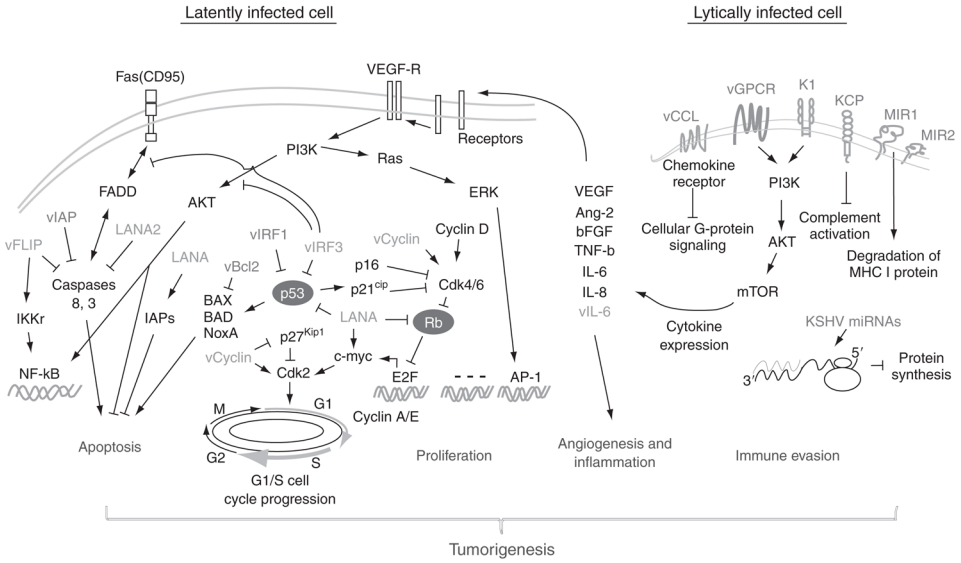

FIGURE 3.

Putative mechanisms of KSHV-mediated regulation of angiogenesis, cell growth and survival, and immune evasion. Cell cycle progression in G1 is controlled by cyclin D/Cdk4/6 complexes which phophorylates Rb. Phosphorylation of Rb leads to Rb inactivation and release transcription factor E2F and transcription of S-phase genes, like Cyclin E and A (Malumbres and Barbacid, 2005). Additionally, p53-mediated Cdk2 and Bax activation and Fas-mediated Caspase activation individually induces cell-cycle arrest and apoptosis. In the latently infected cells, KSHV-encoded latent antigens (green) like LANA and vCyclin drive cell proliferation by targeting two cell-cycle checkpoints: (1) Inactivate Rb to release E2F; and (2) Block p53/$p27^{Kip1}$-mediated cell-cycle arrest (Cai *et al.*, 2006a,b; Friborg *et al.*, 1999; Jarviluoma *et al.*, 2006; Mann *et al.*, 1999). Meanwhile, LANA cooperates with vFLIP to block Caspase and Bax-mediated apoptosis (Sarid *et al.*, 1999). However, in a small amount of lytically infected cells, KSHV encodes some early lytic proteins (orange) like vGPCR vIRF and MIR1/2 or miRNA which dysregulate immune system to produce certain cytokines and help viral infection by angiogenesis and inflammation (Wang *et al.*, 2004).

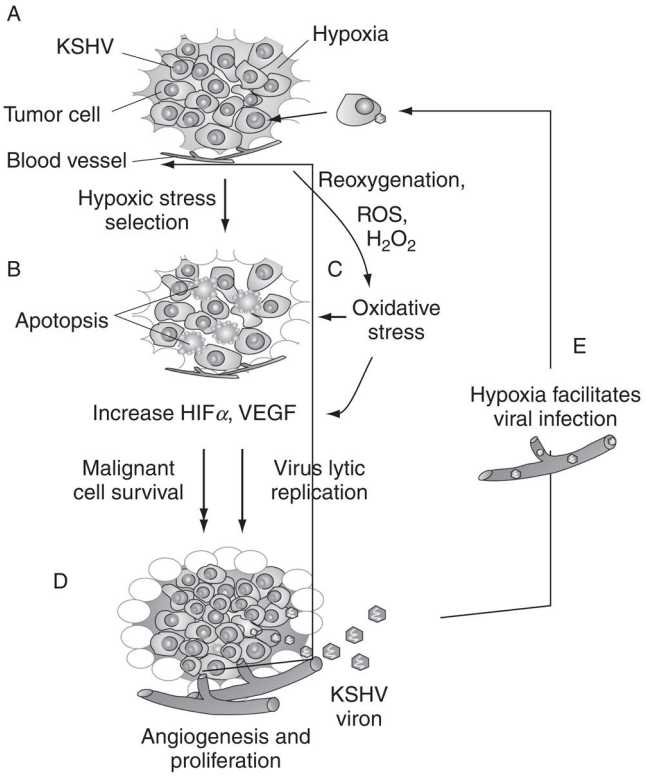

FIGURE 4.

Microenvironmental stress promotes the development of KSHV-mediated malignancy. (A) Proliferation of KSHV-infected tumor cells initiates the formation of hypoxia microenvironment; (B) Hypoxic stress induces cell selection by apoptosis and mutation and increases HIFα and VEGF levels; meanwhile, (C) Oxidative stress caused by reoxygenation or overproduction of ROS also induces similar response as hypoxic stress, and thereby (D) selects the survival of malignant tumor cells to promote angiogenesis and tumor progression. On the other hand, (E) the microenvironmental stresses reactivate KSHV from latent infection to produce new virion particles and help viral primary infection.

TABLE 1

World-wide distribution and divergence of KSHV subtype infection

KSHV subtype	Populations related	References
A	Northern European, Americans, Asian	Lacoste *et al.* (2000), Poole *et al.* (1999)
B	African	Biggar *et al.* (2000), Cook *et al.* (1999), Kakoola *et al.* (2001), Lacoste *et al.* (2000), Meng *et al.* (2001), Poole *et al.* (1999)
C	Northern European, Americans, Asian	Lacoste *et al.* (2000), Poole *et al.* (1999)
D	Old Asian, Polynesian (old pacific island)	Biggar *et al.* (2000), Cook *et al.* (1999), Kakoola *et al.* (2001), Lacoste *et al.* (2000), Meng *et al.* (2001), Poole *et al.* (1999)
E	Brazilian Amerindian	Biggar *et al.* (2000), Cook *et al.* (1999), Kakoola *et al.* (2001), Lacoste *et al.* (2000), Meng *et al.* (2001), Poole *et al.* (1999)
Z	Small cohort of Zambian children	Lacoste *et al.* (2000), Poole *et al.* (1999)

According to K1 differ by 0.4–44%.

TABLE 2

Major cellular homologs encoded by KSHV

Gene product	ORF	Function	Expression pattern
vIL-6	K2	Constitutively activate gp130 independently of IL-6R; B cell proliferation; auto/paracrine growth factors; *angiogenic*	Productive
vCCL1	K6	CCR5 and CCR8 agonists; chemoattraction of Th2 cells and monocytes; *angiogenic*	Productive
vCCL2	K4	CCR3 and CCR8 agonists; chemoattraction of Th2 cells and monocytes; *angiogenic*	Productive
vCCL3	K4.1	CCR4 agonist; chemoattraction of Th2 cells; induction of VEGF-A and *angiogenesis*	Productive
vIAP	K7	Inhibitor of apoptosis; inhibition of vGPCR expression and function	Productive
vBcl-2	ORF16	Inhibition of Bax-mediated and virally induced apoptosis	Productive
vIRF1	K9	Transformation; inhibition of p300, p53, and TGF-β; inhibition of type I interferon	Productive
vIRF2	K11.5	Inhibition of type I interferon and NF-kB; inhibition of Fas-mediated apoptosis via inhibition of CD95L expression	Productive
LANA-2	K10.5	Inhibition of type I interferon production; inhibition of PKR- and caspase 3-mediated apoptosis	Productive
vIRF3	K10.6	Inhibition of p53 and NF-kB; inhibition of Fas-mediated apoptosis via inhibition CD95L expression	Productive
vFLIP	K13/ORF71	Transactivator of NF-kB; antiapoptotic activity via FADD and TRADD binding; *transformation*	Latent
	vCyclin	ORF72	
		Constitutively activate Cdk6; resistant to Cdk inhibitors, destabilizes p27	Latent
vOX-2	K14	Downregulation of myeloid cell activation; regulation of inflammatory cytokine production (IL-1β, TNF-α, IL-8, IFN-γ, and IL-6)	Productive
vGPCR	ORF74	Constitutively active; induces VEGF secretion; *transformation*	Latent/productive