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Molecular Genetics of Kaposi's Sarcoma-Associated Herpesvirus (Human Herpesvirus 8) Epidemiology and Pathogenesis

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INTRODUCTION

In 1872, Moritz Kaposi described an angiomatous neoplasm that affected elderly men of Italian, Jewish, or Mediterranean origin and had a relatively aggressive evolution, a disorder later known as classical Kaposi's sarcoma (KS) (reviewed in reference 216). Years later, other epidemiologic forms of KS were also reported, including endemic KS in equatorial Africa and iatrogenic KS among immunosuppressed organ transplant recipients. In 1981, disseminated and highly aggressive KS in young homosexual men with a poor prognosis was identified as a part of a new AIDS epidemic and was thus termed "epidemic KS" (49, 192, 226). Analyses of numerous American and European human immunodeficiency virus type 1 (HIV-1)-infected populations revealed that up to 30% of HIV-1-positive homosexual men develop AIDS-associated KS (37). Further epidemiologic studies suggested an infectious etiology of this previously rare cancer (37, 528), confirming that the major risk factor is homosexual sex among young men (37, 528).

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Indeed, herpesvirus-like particles in tissue culture of KS specimens from different geographic regions was observed more than 30 years ago (182), and an association with human cytomegalovirus (HCMV) infection had originally been proposed (170, 183). However, the major breakthrough in the hunt for the KS agent came in 1994, when Chang et al. used representational difference analysis to discover two DNA fragments associated uniquely with diseased dermal tissue from a KS lesion of a patient with AIDS (90). Confirming the suspected infectious nature of KS, the sequences did not represent heritable human polymorphic loci but had 39 and 51% amino acid identity to the capsid and tegument proteins, respectively, of two transforming primate gammaherpesviruses, Epstein-Barr virus (EBV) and herpesvirus saimiri (HVS) (90).

Concordant with its homology to lymphotropic viruses, the discovery of KS-associated herpesvirus (KSHV) DNA in KS specimens was soon followed by detection of the virus in cultured cells from patients with primary effusion lymphoma (PEL), a rare AIDS-associated B-cell non-Hodgkin's lymphoma (NHL) (82, 83, 366, 424). The ability of PEL cells to support continuous KSHV infection and conditional, productive replication (342, 355, 424) was crucial for the subsequent cloning and nucleotide sequencing of the entire viral genome (436) and for direct visualization of mature herpesvirus-like KSHV virions by electron microscopy (384, 424, 439). The complete nucleotide sequence of KSHV (also called human herpesvirus-8 [HHV-8]) confirmed its classification as a rhadinovirus, or gamma-2-herpesvirus, joining the gamma-1-herpesvirus EBV as the only human gammaherpesviruses (355, 436). Initial seroepidemiologic studies using PEL cells as a source of KSHV-specific antigen established that all pathogenic forms of KS are associated with infection by KSHV (176, 250, 290, 343, 466). The fascinating epidemiology of KS and the creative molecular virologic studies of KSHV have ignited vigorous interest in this DNA tumor virus. Although the resulting explosion of the literature has brought us closer to understanding the relationship between KSHV replication and the unique malignancies associated with its infection of humans, many questions remain unanswered.

CLINICOEPIDEMIOLOGY OF KSHV

The individual clinicoepidemiologic forms of KS have been classified as classic or sporadic (in the Mediterranean region), epidemic (or AIDS associated), endemic (in Africa), and iatrogenic (in organ and tissue transplant recipients receiving immunosuppressive therapy). Historically, each form has been distinguished by numerous clinical parameters, including the extent of anatomic involvement, the aggressiveness of lesion formation, and associated morbidity and mortality, as well as by divergent patient risk factors, notably age, sex, and ethnogeographic origin (each of these is discussed individually below [452, 549]). Despite these clinical differences, it is now well established that all four epidemiologic forms of KS have in common KSHV infection of the host (12, 13, 161, 176, 250, 290, 343, 390, 412, 419, 449, 466), with the four forms of KS being histologically indistinguishable (1). Seroconversion for KSHV occurs before progression to KS and is a strong predictor of clinical disease (175, 250, 325, 356, 425). The risk of KS in most populations (AIDS and non-AIDS) is directly proportional to the prevalence of KSHV; however, in HIV-uninfected populations, the prevalence varies widely in geographically distinct patterns (35, 176, 290, 382, 412, 466, 531).

Although KSHV infection is a prerequisite for KS development, the clinical disparities between the individual epidemiologic forms of KS suggest a significant role for cofactors in the outcome of infection. For example, coinfection by HIV-1 is clearly the major risk factor unique to AIDS-associated KS and distinguishes its aggressive course from the other forms. However, the pathogenic consequences of genetic variation within the KSHV type species and within different human populations, together with the interactions between them, is not yet well understood. Integration of further epidemiologic studies (e.g., route of transmission) with analyses of molecular genetic host-virus interactions in tissue culture and nonhuman models of infection promise to reveal key mechanisms in the pathogenesis of KSHV.

Classic KS

Classic KS occurs as a rare and indolent form in elderly Mediterranean men, with particularly high incidence in Italy, Greece, Turkey, and Israel (230, 452). Historically, KS incidence in the Mediterranean is up to 10-fold higher than in the rest of Europe and the United States (40, 133, 204). Classic KS lesions tend to remain confined to the lower extremities and preferentially afflict men rather than women, at approximately a 15:1 ratio. Those affected often live with the disease for 10 years or more and are usually not killed by it (216).

In Italy, seroprevalence and incidence increase with age, particularly in males who have reached their 50th birthdays (443). Unlike AIDS-associated KS, HIV-1 coinfection is not typical, but the observation that KS develops annually in only 0.03% of KSHV-infected men older than 50 years in the Mediterranean strongly suggests the existence of a cofactor(s) (516).

Extensive epidemiologic studies in Italy demonstrate a strong influence of ethnogeography on KSHV seropositivity and KS incidence, with a marked gradient increasing from the north to the south. Among a population of 910 blood donors and lymphoma patients, the lowest incidences were in northern Italy (7.3% KSHV positive, 0.605 case of KS/100,000 population/year), the highest incidences were in the south (24.6% and 1.495/100,000), and a moderate number were in central Italy (9.5% and 0.5/100,000) (531). Two particular southern Italian hot spots for KS are on the islands of Sardinia and Sicily: for example, a high rate of KS in northern Sardinia is associated with a general seroprevalence of 35%, with a range of 15.3 to 46.3% in five areas (443). However, hot spots also occur in low-incidence regions: in the Po Valley in northern (mainland) Italy, the incidence is 2.5/100,000 men and 0.7/100,000 women, with one rural zone having double the male rate and four times the female rate (24). Elsewhere in Mediterranean Europe, a group of blood donors in Spain had a low KSHV seropositivity similar to that of northern Italians (171). The high prevalence of KSHV in the Mediterranean contrasts with non-Mediterranean European countries such as Latvia, where a recent screening of 150 healthy blood donors by PCR detected human cytomegalovirus, HHV-6, and HHV-7 but failed to detect KSHV (269).

The indolent nature of classic KS has made the determina-

tion of its prognostic factors challenging, but the geographic gradient of seropositivity would appear to make Italy an ideal setting to identify environmental risk factors. In northern Sardinia, the occupation of cereal farming enhances KS risk (116), lending support to Ziegler's hypothesis that chronic exposure to the aluminosilicate-rich volcanic soils specific to southern Italy may contribute to localized immune suppression in the extremities and increased KS risk (546). However, other studies have failed to confirm the connection between type of soil and KS incidence in northeast Sardinia (350). In the Po Valley, residence in areas where malaria was formerly endemic corresponded to regions of high KSHV seroprevalence (24).

Coluzzi et al. make a provocative argument that many of the risk factors identified for classic KS might be attributable to high exposure of those populations to blood-sucking arthropods (108). The authors hypothesize that local immunosuppression engendered by injection of insect saliva following a bite would prime the tissue microenvironment to enhance (i) transmission of KSHV (from an infected adult's saliva applied as a "salve" to a bitten child) or (ii) reactivation of KSHV in an elderly person, whose immune system is already declining. Although this evidence is largely anecdotal, the authors propose prospective studies to test their hypotheses.

Two other studies explored the risk associated with age and immune function. Brenner et al. (58) retrospectively analyzed all of the classic KS patients (a total of 248) treated in two hospitals in northern Israel and Tel Aviv between 1960 and 1995. Using progression-free survival as the end point of disease, univariate and multivariate analyses showed that increasing age at KS diagnosis was prognostic of increasing disease progression and that immunosuppression (from steroid treatment or renal failure associated with organ transplantation) predicted dissemination. A second study found that KS risk was associated with both mild immunosuppression (lower lymphocyte and $CD4^+$ cell counts) as well as immune activation (increased serum neopterin and β_2-microglobulin levels) (503).

Behaviors that influence KS risk have been examined by Goedert et al., who demonstrated that increased cigarette smoking (measured both in packs per day and in "pack-years") reduces the risk of classic KS fourfold (189). This study used the powerful comparison of patients with both histologically confirmed KS and serologically confirmed KSHV infection to age- and sex-matched controls who were KSHV positive without KS. Topical corticosteroid use, infrequent bathing, and asthma independently increased risk for KS in this study.

Transmission of KSHV in classic KS probably occurs by both sexual and nonsexual routes. Both the close family members and heterosexual partners of KS patients show increased KSHV seroprevalence (19, 56), while a group of 51 Catholic nuns in Italy had a seroprevalence indistinguishable from that of matched female controls (517). Similar to AIDS-associated KS patients, the high frequency of detection of KSHV DNA in tonsillar swabs from HIV-negative KS patients in Italy suggests that transmission in saliva is a predominant route (75). Conversely, only 2 of 27 seropositive Italian women had KSHV DNA in cervicovaginal smears (428). Chemotherapy and/or radiotherapy has been used successfully to treat classic KS in France, but KSHV DNA remains detectable in postlesional skin and peripheral blood mononuclear cells (PBMCs), suggesting a potential explanation for the frequently observed relapse of classic KS (206).

AIDS-Associated KS

KS is the most common neoplasm in homosexual and bisexual men with AIDS (186); the disease is extremely aggressive in this population and displays a more frequent mucosal progression than in the other epidemiologic forms (452). It commonly presents multifocally and frequently on the upper body, head, and neck (216), and it evolves quickly, both in local progression of lesions to tumors and in visceral dissemination leading to organ dysfunction and high mortality.

In the United States, the frequency of dual KSHV- and HIV-positive subjects during the height of the AIDS epidemic corresponded to AIDS epicenters: from 3% in Kansas and 6% in Iowa to 30% in California and 31% in New York (38). The incidence of AIDS-associated KS in homosexual men in San Francisco in the early 1980s was nearly 40% (325), but the decline in new infections reduced its frequency in AIDS patients in the mid-1990s to about 15 to 25% (137, 336, 425). Recent data suggest that KSHV was highly prevalent in the homosexual population prior to the AIDS epidemic: in San Francisco in the first 6 months of 1978, the prevalence of KSHV was 24.6%, with a concurrent HIV-1 prevalence of only 1.8% (386).

Similar to classic KS, the relative seroprevalence of KSHV matches the KS incidence in HIV-infected populations. Serological surveys show that KSHV prevalence is increased in patients with a high risk of developing KS (176, 325, 343, 466) and that infection with KSHV anticipates the development of KS (175, 250, 325, 356, 425, 530). For example, in Thailand, where there is a high prevalence of HIV but a low prevalence of AIDS-associated KS, only 2 to 12% of HIV-1-positive homosexual men were KSHV seropositive (a value only slightly higher than that for the general population in that country) (27). In regions where classic KS is common, such as Rome, patients at a sexually transmitted disease (STD) clinic with the highest relative KS risk were homosexual HIV-positive males (429), also suggesting a coevolving AIDS-related KS epidemic.

A direct correlation between HIV-1 infection, AIDS pathogenesis, and KS progression has been demonstrated in numerous studies. In a cohort of homosexual men from New York and Washington, D.C., 12.5% of men who enrolled with a $CD4^+$ count of <330 cells/μl developed KS while none with a count of >550 cells/μl presented with KS (187). Similarly, other reports have shown that (i) KSHV seropositivity increased as $CD4^+$ counts decreased (325), (ii) detection of KSHV DNA in peripheral blood corresponded to a lower mean $CD4^+$ cell count in HIV-1-positive patients without KS (344), and (iii) KS progression was proportional to an increased rate of $CD4^+$ cell loss and increased HIV-1 RNA levels (233).

HIV-1 probably exacerbates KSHV pathogenesis at multiple levels, including through immunosuppression, by priming of target cells and the tissue microenvironment for KSHV infection and replication, and by exerting direct effects on KSHV gene expression and viral replication. Direct and reciprocal interactions between HIV-1 and KSHV at the molecular level have received a lot of recent attention in the literature; they

suggest mutual positive-feedback loops during replication of both viruses. This is discussed further below.

Many conflicting studies have demonstrated, however, that the relative contributions of HIV-1 burden and immunosuppression to KS development are not always directly proportional. There was no correspondence between $CD4^+$ count and the risk of KSHV seroconversion in a prospective study of 259 Danish homosexual men (336). Likewise, specific T-cell responses to purified KSHV virions were reduced in HIV-1-positive men but were proportional to KS risk in HIV-1-negative men; however, both were independent of $CD4^+$ counts (486). Similarly, there was no correlation between $CD4^+$ count, HIV-1 RNA levels, and KS progression in an AIDS-associated KS cohort in Zimbabwe; instead, KS progression was proportional to the KSHV burden in the peripheral blood (68). Finally, Veugelers, et al. found that age at the time of KSHV seroconversion may carry more risk than absolute $CD4^+$ numbers: older HIV-1-positive men have higher $CD4^+$ numbers at the time of seroconversion than do younger men (512).

Furthermore, in the Amsterdam Cohort, decreasing $CD4^+$ numbers had no influence on the rate of KSHV seroconversion but, instead, correlated with increased KSHV replication; this was suggested by an increase of antibody titers to a viral structural protein but no change in antibody titers to a viral latent protein as $CD4^+$ levels decreased (193). This study also demonstrated that KSHV seroconversion following HIV-1 seroconversion carries a higher risk for KS development than does KSHV seroconversion prior to HIV-1 seroconversion (193). In AIDS-associated KS patients in Italy, a 5.4-fold increase in detectable KSHV DNA in plasma was associated with patients having more than 50 HIV-1 RNA copies per ml of plasma; however, a 7.24-fold increase in detectable KSHV DNA in plasma was correlated with a higher, not a lower, $CD4^+$ cell count (498). Similarly, Quinlivan et al. established real-time PCR as a sensitive, specific method for KSHV detection in PBMCs and demonstrated that the KSHV burden in PBMCs, but not $CD4^+$ counts or HIV-1 RNA, was predictive of KS outcome (410).

Sexual transmission of KSHV in the HIV-infected population is supported by numerous data, and sexual behavior is the most significant epidemiologic variable in AIDS-associated KS (325). The risk of developing KS is >10,000 times higher in HIV-infected homosexuals than in the general population (186). Conversely, hemophiliacs and injection drug users with AIDS have historically had a markedly reduced KSHV prevalence and KS risk (38). Furthermore, the disease is 300 times more frequent in homosexual and bisexual men than in other immunosuppressed individuals (38). Sexual exposure is the strongest risk factor for KSHV infection, and a history of STDs prior to KS diagnosis is strongly associated with KSHV seropositivity (325). Women with AIDS have a fourfold-increased risk of KS if their partners are bisexual rather than addicted intravenous drug users (38).

Recent studies have suggested that orogenital rather than anogenital sex may be the most significant behavioral risk factor for KSHV infection. Although receptive anal intercourse was a KSHV risk factor among homosexual men in the Amsterdam Cohort Study (336), participation in orogenital sex was a predictor for KSHV seroconversion (140). In the period from 1985 to 1996, the HIV-1 seroconversion rate in that population was declining while the KSHV seroconversion rate remained relatively steady. These trends were accompanied by a decreasing percentage of cases of unprotected anal sex with a decreasing number of partners. However, virtually 100% of the population reported at least one occurrence of unprotected oral sex in every year of the study, with an increasing number of partners over that period. Studies of three different populations with high STD and AIDS prevalences in San Francisco agree with this behavioral risk factor, suggesting that insertive oral sex may be the highest risk behavior, as inferred from the easy detection of KSHV in saliva but a low viral load in semen (386). In agreement, many studies have found KSHV in the saliva of seropositive patients (45, 266, 392, 481, 513), and KSHV has been detected in prostate tissue and the male urogenital tract (132, 348, 481, 483); detection of KSHV in the ejaculate has been reported but remains controversial (255, 300, 348, 396, 481; P. Gupta, M. K. Singh, C. Rinaldo, M. Ding, H. Farzadegan, A. Saah, D. Hoover, P. Moore, and L. Kingsley, Letter, AIDS **10:**1596–1598, 1996). Taken together, these studies affirm a route of sexual transmission for KSHV that differs significantly from that for HIV-1. Indeed, 474 HIV-negative men who have sex with men were monitored for 1 year in Seattle and showed a higher seroconversion for KSHV (3.8/100 person-years; similar to that for herpes simplex virus type 1) than for HIV-1 (74).

The increasing and successful use of highly active antiretroviral therapy (HAART) has afforded important clinicoepidemiological insights into the reversal of AIDS and the consequent fate of KSHV pathogenesis. Widespread HAART has resulted in a yearly declining trend in AIDS-related deaths in the United States since 1996 (77a). In agreement, the Centers for Disease Control and Prevention has reported an 8.8% annual decline in KS incidence in the United States between 1990 and 1998 (239). In raw numbers, a cancer surveillance program of the general population in San Francisco has recorded a dynamic incidence of KS over the past 30 years: in 1973 (prior to AIDS), 0.5 KS case per 100,000 people per year was reported; during the AIDS peak from 1987 to 1991, this value increased to 31.1 to 33.3, but then sharply declined to 2.8 in 1998 (post-HAART) (146). Others predict further reductions in KS incidence (501). Reduced KS risk has been associated with triple, but not single or double, therapy (239), and one study showed complete KS remission within 6 months of HAART initiation in 9 of 10 early-stage AIDS-associated KS patients (387). Tam et al. calculated an 81% reduction in risk of death for AIDS-KS patients treated with HAART; the control group consisted of AIDS-KS patients who received no therapy or single or double therapy (495). HAART was also shown to be efficacious if initiated following KS diagnosis (495).

There is clear evidence that immune restoration due to HAART is one key to improving the prognosis of AIDS-KS patients. Over 52 weeks of HAART, 19 AIDS patients demonstrated increased $CD4^+$ counts, increased $CD8^+$ anti-KSHV cytotoxic T-lymphocyte (CTL) activity, and increased anti-KSHV antibody titers (534). This immune restoration was associated with decreased HIV-1 and KSHV viral loads in the blood, and patients without KS at baseline experienced a greater decrease in KSHV load than did patients with KS.

However, patients with KS had a greater number of CTLs specific for lytic viral antigens, suggesting that replication of KSHV is faster in patients with KS than in infected patients without KS. HAART also restores anti-PEL natural killer (NK) cell lytic activity in AIDS-associated KS patients (469). This immune restoration is associated with loss of detection of KSHV DNA in PBMCs in these patients. At baseline, high $CD4^+$ counts and undetectable KSHV DNA in PBMCs are predictive of HAART success in KS regression (395).

HAART may reverse KS progression not only by inhibiting HIV-1 replication but also by exerting direct effects on KS tumors. The HIV-1 specific protease inhibitors (PIs) indinavir and saquinavir have recently been demonstrated to inhibit angiogenic lesion formation by primary AIDS-associated KS cells and injected basic fibroblast growth factor (bFGF) in nude mice (459). The PIs were also antiangiogenic in chorioallantoic membrane (CAM) assays and blocked the invasion of modified human umbilical vein endothelial cells (HUVECs) in in vitro assays. Mechanistic studies demonstrated that the PIs inhibited cleavage and activation of matrix metalloprotease-2 (459), a protein that is highly expressed in human KS lesions (502) and is required for basement membrane degradation prior to endothelial cell invasion; interestingly, the PIs did not directly inhibit the cleavage of matrix metalloprotease-2 but instead acted upstream.

As expected, lack of response to HAART is associated with AIDS-associated KS progression: 2 of 14 non-HAART responders among Italian AIDS-associated KS patients failed to show a reduction in HIV-1 RNA load or an increase in $CD4^+$ numbers; consequently, their KS progressed (77). Nonresponders also failed to recover NK activity with respect to cells latently infected with KSHV (PEL cells) and failed to clear KSHV from PBMCs (469). A case report clearly demonstrated the inverse relationship between HAART and KS: after 6 years of antiretroviral therapy, including 3 years of HAART, KSHV DNA became undetectable in PBMCs (388). However, a 2-month interruption of HAART in this patient resulted in a rapid rebound of KSHV seropositivity and viral DNA load. HAART was subsequently reintroduced, and KSHV peripheral DNA became undetectable after 4 months. Considering only current therapies, the fate of AIDS-associated KS in dually infected patients will arguably depend on the continued success of HAART treatment.

Endemic (African) KS

Prior to the emergence of HIV, African KS was an endemic disease that affected mainly two age groups: young men with an average age of 35 years and children with an average age of 3 years (519). In Cameroon from 1986 to 1993, the latter form accounted for about 4% of childhood cancers (247). The highest prevalence of African KS prior to AIDS was found in a broad band crossing equatorial Africa, with particularly high rates in northeastern Zaire and western Uganda and Tanzania. This geographic pattern conformed to areas of frequent podoconiosis, a lymphatic disease of the legs presenting as lymphedema etiologically associated with chronic, barefoot exposure to volcanic soils (548). In podoconiosis, microparticles of silica dust in these soils penetrate the skin of the foot during barefoot walking and are then taken up by the lymphatics and cause localized inflammation and lymphedema. Aluminosilicates are cytotoxic to macrophages in animal models (168) and may contribute to localized immune suppression; this had been proposed as an environmental contributor to African KS (548).

However, KS on that continent has evolved to an epidemic magnitude as the spread of the AIDS pandemic has exacerbated the already elevated prevalence of endemic KS. Current clinicoepidemiologic studies of African KS as an independent disease entity are thus virtually impossible in most contemporary African populations.

Clinically, KS in Africa is more frequent in children (247, 526, 547) and females than anywhere else worldwide and occurs in four forms (216). One form is similar to classic KS in its course but strikes young adults. The other three forms are more aggressive and are similar to AIDS-associated KS in their progression: one of these, however, remains cutaneous with local tissue invasion, while another occurs most often in young children with a mean age of 3 years, is aggressive with visceral progression, but often lacks the cutaneous involvement (216). In Tanzania, the highest incidence of pediatric KS was in children younger than 5 years, possibly reflecting a low resistance to KSHV infection (14). Among children in Africa, there are age-specific discrepancies in clinical course: comparing Zambian children over the age range of 3 to 15 years, the younger patients presented primarily with lymphadenopathy while the older patients had cutaneous involvement (247).

A comparison of the prevalence of KS prior to AIDS with its prevalence during the AIDS pandemic in Africa clearly demonstrates the brutal potentiation of KS by HIV-1 coinfection. In the pre-AIDS periods from 1954 to 1960 and 1968 to 1970 in Uganda, KS was diagnosed in 6.4 to 6.6% of male cancer patients, respectively, with no female cases. However, in 1989 to 1991, KS prevalence in male cancer patients rose to 48.6% (incidence of 30.1/100,000), becoming the most frequently reported cancer in men, while prevalence in female cancer patients climbed to 17.9% (incidence of 11.0/100000) (519). KS is also the leading cancer in Zimbabwe, comprising almost 33% of cancers there (102), and accounts for 15% of male cancers in Zaire (376). Since the emergence of AIDS, the incidence of KS in children has increased 40-fold in Uganda (547), while in South African women it has increased at a higher rate than in men: the male-to-female ratio has decreased from 7:1 in 1988 to 2:1 in 1996 (471). Paradoxically, calculations of the relative risks of KS in HIV-1-positive patients in Rwanda, Uganda, and South Africa were 35, 62, and 54, respectively, much lower than that in the United States and Europe (approximately 300); Sitas and colleagues hypothesized, however, that the cumulative risk relative to the West was similar due to the higher pre-AIDS prevalence of KS in Africa (472). In the rare countries where the KS incidence has not dramatically changed since AIDS, the progression of the disease remains dramatically altered; for example, in Tanzanian children, the overall incidence and the ratio of KS in boys to girls (about 5:1) have remained consistent pre- and post-AIDS, but the anatomical distribution now typically resembles that of more aggressive KS (14). Overall, while the prevalence of KS within the HIV-positive community has skyrocketed, even the prevalence of KS in the HIV-negative, "contemporary"-endemic population has risen.

Despite clinical heterogeneity, all forms of KS in Africa are

associated with KSHV infection (62, 92, 104, 176, 290). HIV-1-positive South African patients have shown higher titers of antibodies to KSHV latent proteins than have HIV-1-negative patients and have had a higher risk of developing KS (470). KSHV seropositivity in Africa is quite heterogeneous geographically, ranging from 36 to 100% in different countries and populations in sub-Saharan Africa (reviewed in reference 93). Similar to the situation for U.S. populations, numerous studies support the inference that KSHV was highly prevalent preceding the emergence of HIV-1; nonetheless, these studies affirm the critical role of HIV-1 as a cofactor in African KS progression. For instance, the age-specific prevalence of KSHV in Uganda has been virtually unchanged over the period of enormous increases in KS incidence during the emergence of AIDS (129). Interestingly, studies of Gambians suggest that those coinfected by HIV-1 have a 12.4-fold higher risk of KS development than those coinfected by HIV-2, even with equal seroprevalence for KSHV in the two groups (22).

Unlike the strict correlation between KSHV prevalence and disease incidence in Western countries, however, different African populations that have similar KSHV prevalences may have significant variations in KS incidences. For example, a cohort of 249 Ethiopian immigrants to Israel had KSHV seroprevalence typical of many African countries: 39.1% in HIV-negative people and 57% in HIV-positive people, yet none developed KS (201).

The endemic pattern of KS in Africa, especially the high prevalence in childhood, reflects the occurrence of primary KSHV infection before puberty (including during infancy). In fact, in many African populations, seroprevalence reaches adult levels during adolescence. During the AIDS epidemic in Uganda, 37% of children younger than 5 years were seroreactive to at least one KSHV antigen, and this proportion increased to 58% in children 5 to 9 years old and leveled off at an adult-like level of 49% after the age of 20 years (331). These authors noted that this pattern of prepubescent acquisition of KSHV infection is similar to that seen for EBV and hepatitis B virus in many African countries. A pre-AIDS population in Uganda showed a similar trend, but the overall KSHV seroprevalence was higher, reaching 57% at 11 to 13 years old, 89% at 14 to 17 years old, and 84% at 23 to more than 50 years old (129). In Cameroon, seroprevalence increases gradually during childhood to 48% by the age of 15 years, nearly equal to the seroprevalence among pregnant women (54.5%) living in similar areas (180). Similarly, the seroprevalence of anti-lytic antibodies to KSHV in Egyptian children increased from 16.6% at younger than 1 year to 58% at older than 12 years; however, there was no consistent increase in the levels of antibodies to latent KSHV proteins (16).

This early appearance of KSHV in children in Africa suggests that transmission is primarily nonsexual, possibly occurring from mother to fetus (142), with clear evidence of intrafamilial and horizontal spread. Indeed, a significant risk factor for seroconversion of a child is having a KSHV-infected mother: 42% of children born to seropositive mothers were also seropositive when tested between 0 and 14 years of age, while only 1% of those born to seronegative mothers were seropositive (53). In this study, the potential for vertical transmission of KSHV was suggested, since one of four infants younger than 18 months born to an infected mother was also seropositive.

However, many studies argue that a majority of seropositive infants acquire maternal immunoglobulins passively from their mothers, with vertical transmission of virus remaining possible but rare. For example, 83% of Zambian infants were KSHV seropositive if born to a mother who was also seropositive; however, only 3% of the infants had detectable KSHV DNA in their PBMCs (322). Frequent studies have demonstrated a loss of KSHV seropositivity in children after infancy. A total of 46% of infants in Cameroon were seropositive prior to 6 months of age, but only 13% were seropositive between 7 and 12 months of age (180). A total of 25 and 58% of Ugandan infants were seropositive in two studies, but at 1 year old, none were seropositive (129, 331), and 14 infants born to HIV- and KSHV-positive mothers were also seropositive before 1 month of age, but all had lost seropositivity by 6 months old (316). Outside of Africa, similar results have been reported for 32 HIV-1-infected mother-infant pairs of Ghanian and Italian descent (67).

Childhood transmission in Africans therefore seems to follow mostly horizontal patterns, with a few vertical instances. An increasing risk of KSHV infection in Egyptian children (detected by serologic or DNA testing) is proportional to having contact with more than two other children or with having siblings (18). A unique perspective on intrafamilial transmission of KSHV has come from a study of the Noir-Marron of French Guiana, who are descendants of African slaves (403). The seroprevalence rate there reached a plateau of about 15% by 15 years old and then rose sharply to about 30% after the age of 40 years. Intrafamilial correlations of seropositivity were calculated and showed a high correlation between (i) children and their mothers, but not their fathers, and (ii) children and their siblings. The mother-child correlation was even greater for children younger than 10 years old.

Other evidence suggests that transmission in Africa can also occur by population-delimited routes. Blood-borne transmission has been suggested for an Eritrean tribe that has detectable KSHV DNA in serum and practices ritual skin piercing (148). In Djibouti, although street prostitutes have a vastly higher rate of HIV-1 infection than do women who are not prostitutes, the two populations have a very similar KSHV seroprevalence, suggesting different risk factors for transmission of KSHV and HIV-1 there (323). In South Africa and Kenya, seroprevalence does not plateau during puberty, but continues to rise throughout life (470), similar to that of hepatitis B virus (352).

Iatrogenic KS

Iatrogenic KS represents an additional clinicoepidemiologic peculiarity of KSHV infection that presents either chronically or with rapid progression (216). The induction of iatrogenic KS by immunosuppressive therapy and its subsequent regression on removal of immunosuppression provided some of the earliest clinical recognition of the reversibility of KS (216). Iatrogenic KS shows extreme ethnogeographic associations, occurring in only about 0.4% of transplant patients in the United States and Western Europe (157, 398) but in about 4.0 to 5.3% of renal transplant patients in Saudi Arabia (399, 411). Strikingly, KS represents 87.5% of posttransplantation neoplasia in Saudi Arabia (412), and a recent study found KS in 80% of

posttransplantation cancers in Turkey (141). In the latter study, KS developed within 1 year in 46% of those cases. The high frequency of iatrogenic KS in Saudi Arabia reflects the 7% endemic seroprevalence of KSHV in healthy Saudi donors or patients with non-KS malignancies (412). Interestingly, transplant-associated KS is seen predominantly in kidney allograft recipients and not other solid-organ or bone marrow transplant recipients (230); kidney recipients have a greater than two-fold-higher seroprevalence than those at low risk of KS in France (85). Although Andreoni et al. found that 21.4% of liver recipients, but only 8.6% of kidney recipients, seroconverted for KSHV, the risk of KS was higher in the kidney transplant recipients. In fact, 75% of those who progressed to KS were KSHV seropositive prior to transplantation (17).

Differences in immunosuppressive therapy might favor KSHV reactivation in the kidney recipients. KS has historically been seen more often in patients whose treatment includes cyclosporine (397), a drug that can reactivate KSHV from latency to lytic replication in tissue culture (225). Likewise, remission of iatrogenic KS on cessation of immunosuppression is the norm. A recent study in Turkey demonstrated that 8 of 11 iatrogenic KS patients showed complete regression of visceral and cutaneous KS within 6 months of cessation of cyclosporine (141). A recent case study showed regression of cutaneous and mucosal KS after cessation of immunosuppressive therapy in a kidney allograft recipient; however, KSHV DNA persisted in the regressed lesions (367).

A more comprehensive association between KSHV infection and kidney disease was suggested by a study that demonstrated 93% KSHV seroprevalence in Saudi patients with posttransplantation KS, 28% in transplant patients without KS, and 29% in patients with end-stage renal disease (412). In fact, end-stage renal disease and kidney dialysis were found to be risk factors for KSHV seropositivity (11). In a case report, Sarid et al. proposed that the kidney may be a site of latent KSHV, describing two KSHV-seronegative patients who received infected kidney tissue, seroconverted, and subsequently developed KS; a third patient was weakly seropositive prior to transplantation and seemed to reactivate a latent KSHV infection within 1 year (445).

Many data support the inference that most iatrogenic KS patients are KSHV positive prior to transplantation, suggesting that reactivation of latent viral infection leads to disease. One study demonstrated that 10 (91%) of 11 kidney or heart transplant patients who developed iatrogenic KS were KSHV positive prior to their procedures (390). Cattani et al. calculated a relative risk of 34.4 for kidney recipients who were KSHV seropositive versus seronegative prior to transplant (76). In a transplant cohort in Paris, 8% of 400 kidney transplant recipients were KSHV positive prior to transplantation: 28% of these developed KS within 3 years of their procedures, but none of those who were seronegative prior to receiving the kidney developed KS (165). Females, Africans, or those with severe bacterial and/or *Pneumocystis carinii* infection had the highest risks for KS development in that population. Female sex as a risk factor was also found in an Italian cohort and reflected a higher seroprevalence in women than in men prior to transplantation (17). Four of five transplant recipients in Pittsburgh, Pa., who were seropositive prior to transplantation showed a greater than fourfold increase in antibody titer to lytic KSHV antigens (235), supporting the inference of viral reactivation in seropositive organ recipients. Although less frequent, seroconversion following transplantation suggests that seronegative recipients can be infected by KSHV from the donated organ (390).

OTHER KSHV-ASSOCIATED DISEASES

As discussed above, epidemiologic proof that KSHV is the etiologic agent in all clinical forms of KS has come largely from universal detection of viral nucleic acids in diseased but not healthy tissue and from direct correlations between detection of KSHV, risk of developing KS, and progression to disease. Epidemiologic proof that KSHV infection is etiologically associated with diseases other than KS in the HIV-negative population, however, has been more elusive. For example, in the absence of AIDS, a second KSHV-associated cancer, PEL, is extremely rare, thus frustrating attempts to establish statistically significant correlations with KSHV infection. The etiologic connection between PEL and KSHV infection has thus relied on the HIV-positive population. Although PEL is rare even in AIDS patients, constituting only 0.13% of all AIDS-associated lymphomas in the United States, previous KS diagnosis confers an increased risk of PEL relative to all other AIDS-associated NHLs (332). Nonetheless, the term "classic PEL" has been coined by Ascoli et al. to describe 20 cases of PEL in HIV-negative elderly patients of Eastern European/Mediterranean and Jewish descent (25), two populations with high seropositivity for KSHV and elevated incidence of classic KS.

KSHV infection may also be associated with heart disease. Classic PEL patients show a high incidence of congestive heart failure, a condition shared with classic KS patients (25). Inversely, Italian patients with cardiovascular disease have a higher KSHV seroprevalence than does the general population (72). Furthermore, HIV-1-positive patients with KS had an increased odds ratio of 3.35 for developing atheroma relative to those without KS (195). In animal models of heart disease, two non-human gammaherpesviruses, murine herpesvirus 68 and bovine herpesvirus 4, both accelerate atherogenesis (7, 305), with the former requiring hyperlipidemia. Furthermore, macaques coinfected with rhesus rhadinovirus and simian immunodeficiency virus frequently develop large-vessel arteritis (321). Interestingly, a KSHV-encoded chemokine, viral macrophage inflammatory protein 1 (vMIP-1), is chemotactic for endothelial cells expressing its receptor, CC chemokine receptor 8 (CCR8) (214). CCR8 is itself expressed on KS spindle cells, as well as on endothelial cells found in atherotic plaques; thus, vMIP-1 may be mimicking the action of its cellular counterpart, the chemokine I-309, which is released by endothelial cells in response to the atherogenic apolipoprotein A (214).

Apart from KS and PEL, KSHV is also variably found in patients with multicentric Castleman disease (MCD) (111, 479), a rare angiolymphoproliferative disorder. More than 90% of patients with AIDS and MCD are infected with KSHV, while no more than 40% of HIV-seronegative MCD patients are infected (196). In MCD lesions, LANA-1 is found in immunoblasts around the hair follicle (142). The ratio of lytically infected to latently infected cells in MCD is much greater than in PEL or KS, suggesting that the pathogenic role of KSHV in

these different diseases might be attributable to different gene expression programs of the virus (196, 249, 380, 389, 431, 482, 499). Furthermore, the occurrence of MCD increased the risk of subsequent NHL development in an HIV-positive population, hypothetically by (i) clonal expansion of a lesional MCD cell or (ii) oncogenic stimulation of a pre-NHL cell in the MCD microenvironment (379). In this study, in fact, 9 of 14 subjects had concurrent KS, MCD, and PEL.

Other clinical conditions have also been connected with KSHV infections, including angiosarcoma (333), angiolymphoid hyperplasia with eosinophilia (211), skin carcinomas (squamous cell carcinoma and Bowen disease) in immunosuppressed individuals (416), sarcoidosis (131), multiple myeloma (MM) (427), pemphigus vulgaris and pemphigus foliaceus (337, 338), AIDS-associated immunoblastic lymphoma (149), primary central nervous system lymphoma (190), posttransplantation lymphoproliferative disorders (244, 329), and pulmonary inflammatory myofibroblastic tumor (191). A condition of immunocompetent patients named germinotropic lymphoproliferative disorder, in which KSHV- and EBV-coinfected B-cell plasmablasts invade lymphoid follicle germinal centers, has also been described (139).

The etiologic connection between KSHV infection and most of these disorders, however, has not been confirmed: these disorders include skin carcinomas in noncompromised patients (2; N. Dupin, I. Gorin, J. P. Escarde, V. Calvez, M. Grandadam, J. M. Huraux, and H. Agut, Letter, Arch. Dermatol. **133:**537, 1997), angiosarcomas (299), MM (117, 328, 497), mycosis fungoides (217), paraneoplastic pemphigus, pemphigus vulgaris, and pemphigus foliaceus (107).

The connection between KSHV infection and multiple myeloma (MM) has been extremely controversial. KSHV DNA has been detected more frequently in bone marrow stromal cells and fractionated PBMCs enriched for dendritic markers in MM patients than in healthy controls (33, 39, 427). However, only 1 of 15 serologic studies (173) has demonstrated increased anti-KSHV reactivity associated with MM patients (reviewed in reference 496), and MM patients with strong anti-EBV CTL responses unanimously failed, nonetheless, to demonstrate CTL responses to KSHV open reading frame 65 (ORF65) or ORF73 proteins (57). Furthermore, the specific detection of KSHV DNA in MM but not healthy (control) donors has not been confirmed for all populations studied (496).

CLINICAL DETECTION OF KSHV, AND ESTIMATES OF INFECTION IN THE GENERAL POPULATION

Serologic methods have remained the most sensitive approach for detecting exposure to and infection by KSHV since their first use in cementing the etiology of KS. The genesis of KSHV seroepidemiology came from studies employing easily cultured, uniformly KSHV-infected B-lymphoma cell lines (PEL cell lines) as the source of viral latent antigen (176, 250, 355). PELs have since served as the primary target for indirect immunofluorescent-antibody (IFA) approaches to measure levels of antibody to both latent and lytic KSHV proteins in clinical serum samples and have been successfully used as a source of protein extract in confirmatory immunoblots (93, 175, 176, 250, 290, 343, 355, 474, 545). When clinical sera are incubated with latently infected PEL cells or nuclei, they are scored positive for previous viral exposure if a characteristic punctate nuclear stain is observed (176, 250, 355). Very elegant experiments identified this putative latency-associated nuclear antigen (LANA-1 or LNA-1) as the product of the KSHV ORF73 gene, which is sufficient to generate the punctate stain when overexpressed in uninfected 293HEK (human embryonic kidney) cells (252, 253, 355, 417). Among other functions (discussed below), LANA-1 maintains the latent viral genome as a stable episome (30, 115). KSHV virions purified from induced PEL cells have been used as targets in enzyme-linked immunosorbent assays (ELISAs) (94), and publication of the KSHV sequence has allowed rational design of whole-protein and peptide-based ELISAs (87, 304, 413, 450, 466).

The plethora of diagnostic KSHV methods has revealed that the choice of viral antigen can profoundly influence the quantitation of seroprevalence (93, 414). While the prevalence of KSHV in populations with KS (and PEL) is consistently measured at 90 to 100%, the frequency of the virus in the general population has been reported to vary over a wide range. The relative seroprevalences calculated for geographically distinct populations remains consistent if similar antigens are compared between groups (414). However, intrageographic measurements are typically higher when the prevalence of anti-lytic antibodies, as opposed to anti-latent antibodies, is measured (93). For example, 20% of one U.S. cohort of blood donors were seropositive for anti-lytic antibodies but none of the donors were seropositive for anti-latent antibodies (290). Likewise, a Swedish cohort showed 33% anti-lytic but only 6% anti-latent seroreactivity (147). In the general population of the countries of Western Europe, seroprevalence ranges from 2.0 to 4.0% when measured by latent IFA assay, which corresponds to the frequency of KS in those countries (142).

Such discrepancies in measures of seroprevalence have fomented controversy concerning the need to screen donated blood for KSHV. A study of blood samples from blood donors in Texas, using both anti-latent and anti-lytic tests, showed an overall KSHV seroprevalence of 15%, much higher than anticipated from samples in the general American population and reflective of a possible need for screening blood donors in America (28). Blood-borne transmission was also supported by a prospective study of HIV-infected women in the United States that identified intravenous drug use as the most significant risk factor for KSHV seropositivity, with the frequency of intravenous drug use being proportional to the risk (70). However, two studies using identical anti-latent IFA assays to test both donor and recipient blood demonstrated no transmission of KSHV from seropositive donors to seronegative recipients (150, 383). Determinations of the age association with KSHV transmission also suffer from the same discrepancies: healthy children outside Africa have shown reactivity to lytic antigens but are often seronegative for latent antigens (290, 458).

Some experts have proposed that the seemingly increased sensitivity of anti-lytic viral antigen methods may come at the expense of decreased specificity (93). However, recent studies using recombinant KSHV proteins suggest that the lytic glycoprotein K8.1 is more sensitive and specific as a diagnostic antigen than is the latent LANA-1 protein (229). The proteins were expressed by infection of BHK-21 cells with recombinant Semliki Forest virus vectors, and the study also revealed that recombinant K8.1 was 100% specific compared to PEL-based

lytic assays. An ELISA based on a four-branch, multiple antigenic peptide derived from K8.1 likewise demonstrated high sensitivity and specificity (282).

A study that comprehensively compared multiple diagnostic methods suggested that a combination of anti-latent and anti-lytic assays will provide the best diagnostic procedure for detecting KSHV serologically. In a search for the "gold standard" for KSHV detection and KS prediction, Schatz et al. compared six PEL-based IFA assays and eight ELISAs (with whole-protein and optimized peptide antigens) to detect both latent and lytic antigens and found that a dual, anti-lytic/anti-latent IFA assay showed a good balance of specificity (89.1%) and sensitivity (94.9%) (450). A whole virus ELISA followed by a PEL-based IFA assay also showed specific and sensitive results (73).

Of course, PCR-based methods have also been employed successfully to detect KSHV. In clinical samples, viral copy number is highest in affected skin, followed by saliva and PBMC (277), and PCR of KS lesions (among other tissues) gives the highest specificity for diagnosis (124, 277). The detection of KSHV DNA in both PBMCs (277, 395) and plasma suggests that both cell-associated and plasma viremia may contribute to viral dissemination. However, one study detected KSHV DNA unanimously in the plasma of all 14 participants but in the PBMCs of only 1 donor, suggesting that plasma viremia is a better indicator of active replication (498). Overall, the relatively high titers of KSHV in peripheral blood but the virtual lack of evidence for blood-borne transmission suggests that blood is an inefficient tissue for transmission.

In general, many studies agree that serologic testing for KSHV is far more sensitive for detecting infection than is PCR, especially during latency. Early studies estimating the time from detection of infection to appearance of KS strikingly demonstrate this difference. Kaplan-Meier estimates showed that HIV-1-positive men who were seroreactive to LANA-1 at baseline had a 49.6% probability of developing KS 10 years later (i.e., a median time of 10 years) (325). However, quantitation of KSHV DNA in peripheral blood estimated the median time to KS as 3.5 years (530), suggesting that the detection of viral DNA required a higher viral burden and a more advanced infection than detection of seroreactivity. Comparison of the sensitivity of the two detection methods has thus provided insight into relationships between the stage of infection (primary, latent, and lytic) and KSHV pathogenesis. In general, a patient who is seropositive without detectable DNA in the peripheral blood is considered to be carrying a latent KSHV infection (175, 466), whereas seronegative patients who are DNA positive are hosting an early primary infection (18, 523); by inference, those who are positive by both tests have a reactivated infection or a late primary infection.

PRIMARY INFECTION BY KSHV

Unlike reactivation of KSHV from latency, virtually all current studies have demonstrated that primary infection by the virus is not associated with significant concurrent morbidity in immunocompetent populations. The vast majority of prospective studies of primary KSHV infection have evaluated populations of children. Of 53 Zambian children presenting with their first febrile illness and accompanying respiratory symptoms, 4 had KSHV DNA detectable by semiquantitative PCR in whole blood at levels suggesting active viremia (247). Two of the KSHV-positive children were negative for HHV-6 (a common cause of childhood fever), suggesting that their symptoms may have been attributable to a primary KSHV infection. Of 56 Japanese children who presented with acute febrile illness, including many younger than 2 years, 36 (64%) had PCR-detectable KSHV DNA in PBMCs (although these authors implicated bacterial infections as the pathogenic culprits) (257). Of 81 Egyptian children with acute febrile illness, 6 were KSHV seronegative but had KSHV DNA in plasma or saliva, suggesting primary infection; 5 of the 6 also showed a cutaneous craniocaudal maculopapular rash (18). Primary infection can (rarely) occur vertically, and viral DNA has been detected in Zambian infants within their first 24 h of life (322).

Measurements of seroconversion in infants to assess primary KSHV infection are problematic due to the observation that infected mothers passively transfer anti-KSHV antibodies to their offspring (see discussion, above) (67, 129, 180, 316, 331). However, seroconversion can be temporally compared to other clinical parameters and symptoms in order to monitor the natural history of KSHV infection in adults. The first prospective study of primary KSHV infection in immunocompetent adults found that symptoms were similar to those of primary infection during childhood. In a cohort of HIV-negative homosexual men in Pittsburgh, 5 of 108 seroconverted for KSHV (as determined by measuring anti-lytic antibodies) over a 15-year period (523). Their symptoms were fever, diarrhea, fatigue, localized rash, and lymphadenopathy; the first detection of KSHV DNA preceded seroconversion and coincided with the appearance of a broad CTL response to at least three viral lytic proteins in each patient. The CTL response then declined over several years, while viral DNA was persistent and sporadically detectable. Unlike mononucleosis following primary EBV infection, there was no detectable expansion of $CD8^+$ cell numbers during these episodes of KSHV infection. The low KSHV seropositivity in the general population of the United States and western countries suggests that primary infection is not acquired during childhood but, instead, is acquired in sexually mature adults in those regions.

Symptoms of primary KSHV infection in immunosuppressed hosts obviously are more difficult to directly attribute to infection by KSHV. However, a case report of an HIV-1-positive male noted seroconversion to KSHV 5 weeks prior to the sudden onset of symptoms including fever, arthralgia, cervical lymphadenopathy, and splenomegaly (381). PCR of the cervical mass specimen revealed KSHV DNA, vascular hyperplasia, and "intense" activation and proliferation of B cells and was negative for EBV gene expression. The febrile episode was prolonged but resolved spontaneously within 2 months.

Primary infection by KSHV in different immunosuppressive settings may lead to drastically different outcomes. In the Amsterdam cohort, patients who seroconverted for KSHV following HIV-1 seroconversion experienced a greater relative risk for progression to KS than did those who had seroconverted for KSHV prior to HIV-1 infection (193). This suggests that primary KSHV infection has a higher morbidity in those who are HIV-1 infected than in those who reactivate a previous, latent KSHV infection. However, primary KSHV infection during iatrogenic immunosuppression following organ trans-

plantation carries a lower risk for KS than does reactivation of a previous infection (235). It is plausible that these differences in risk of KS following primary infection in the two populations reflect drastically different titers of KSHV in the respective inocula. For example, transmission in the homosexual population is likely to be through saliva, a site of viral shedding that contains high-titer KSHV, potentially from an infected person who is immunosuppressed himself. Conversely, transmission from immunocompetent organ donors is likely to occur via blood, a tissue shown not to be a significant source of virus (150, 383).

HISTOPATHOGENESIS OF KS AND ITS RELATIONSHIP TO KSHV INFECTION

KS lesions contain a variety of cell types, including endothelium, extravasated erythrocytes, infiltrating inflammatory cells, and characteristic "spindle" cells (154). The spindle cells express markers of both endothelium and macrophages (364, 420, 505, 506). The spindle cell population in vivo may be heterogeneous, especially early in KS disease: although a marker specific to fibroblasts and macrophages is expressed on 100% of cultured KS spindle cells, it is expressed on only a subset of cells in situ in KS specimens (465).

Whether spindle cells are derived from vascular or lymphatic precursors has been controversial (143, 240, 270, 318, 529, 539). A new monoclonal antibody that recognizes an O-linked sialoglycoprotein reinforces the argument for a lymphatic origin of these cells. This antibody stains (i) lymphatic, but not vascular, endothelium in normal tissues and (ii) transformed tissues of lymphatic but not vascular origin (241). In cutaneous KS specimens, this antibody stains 100% of the spindle cells from all pathologic stages of KS.

Extensive and aberrant neoangiogenesis in KS lesions is accompanied by elevated levels of many cytokines, including bFGF, interleukin-1 (IL-1), IL-6, IL-8, platelet-derived growth factor, tumor necrosis factor (TNF), gamma interferon (IFN-γ), and vascular endothelial growth factor (VEGF) (reviewed in reference 154). Many of these cytokines are secreted by spindle cells, are essential for spindle cell viability in culture, and are themselves proangiogenic (152, 153, 370), suggesting that maintenance of KS lesions in vivo is dependent on the dysregulation of these growth factors in the tumor milieu. Although elevation of the levels of these cytokines is detectable in the microenvironment of the tumor specimens and is critical in KS pathogenesis, their concentrations in serum do not necessarily correlate with KSHV status or KS incidence (326, 426).

Early PCR-based studies confirmed that KSHV DNA is specifically found in lysates only from affected tissue from KS patients (12, 13, 90, 354, 449). The lymphotropism of KSHV was demonstrated by PCR amplification of viral DNA from the $CD19^+$ B-cell subset of PBMCs from AIDS-associated KS patients (13, 340), as well as in PEL specimens (80, 161, 245, 267, 366), suggesting a mechanism by which the virus may disseminate in the host. Active KSHV replication and increased detection by PCR of viral DNA in the peripheral blood are strongly correlated with (i) increased risk of progression to KS (13, 530) and (ii) increased severity of pathogenic stage of KS (47, 68); the peripheral viral load predicts the pathogenic outcome of the infection (410). KSHV has also been found in the neutrophil subset of PBMCs (285) and in circulating KS-like spindle cells that express markers of both macrophages and endothelium (60; M. C. Sirianni, S. Uccini, A. Angeloni, A. Faggioni, F. Cottoni, and B. Ensoli, Letter, Lancet **349:** 255, 1997).

Localization of KSHV DNA was demonstrated in clinical specimens by PCR in situ hybridization (PCR-ISH); when using this technique in combination with immunohistochemistry of tissue-specific protein expression, Boshoff et al. demonstrated specific KSHV signals in vessel endothelial cells and the majority of spindle cells in cutaneous KS nodule specimens (52). However, KSHV may also infect nonendothelial cells in KS lesions: by using limited tryptic digestion, Foreman et al. used in situ PCR to detect KSHV DNA in epidermal keratinocytes in four of five KS lesions and eccrine (salivary) epithelia in two of four KS lesions (161). Reverse transcription-in situ PCR for KSHV nucleic acid has recently been used to successfully differentiate KS from dermatofibromas and to diagnose KS in two of eight atypical vascular lesions (375). Stamey et al. have demonstrated the successful use of real-time PCR in detection and quantitation of KSHV in KS tissue (481).

Expression of KSHV genes in clinical specimens from all stages of histologically recognizable KS was revealed by ISH with RNA probes (483). More than 85% of the spindle cells in these tumors expressed transcripts from the latent kaposin gene (540), encoding a transforming protein (362) that stimulates the guanine-nucleotide exchange activity of cytohesin-1 upstream of mitogen-activated protein kinase pathways (263; also see discussion below). About 10% of the spindle cells expressed both delayed early (nut-1/PAN) and late (major capsid protein [MCP]) lytic transcripts suggesting that a minor population of tumor cells supports productive viral replication (483). A later study used ISH with a more extensive array of probes to confirm this relationship between latent and lytic gene expression in KS tissue (489). Interestingly, two viral genes encoding cytokine homologs (viral IL-6 [vIL-6] and vMIP-1) and one encoding an anti-apoptotic protein (vBcl-2) were expressed exclusively in cells supporting lytic viral replication, suggesting that the KSHV lytic cycle may directly contribute to the pathogenesis of KS tumors (489). A similar approach was used to detect viral lytic transcripts in lesional monocytes, suggesting a second mechanism, exclusive of B lymphocytes, for viral dissemination (46).

Immunohistochemistry also demonstrated that detection of LANA-1-positive cells in KS lesions increases during progression to nodular KS (143). LANA-1 was detected in cells surrounding slit-like vascular spaces and colocalized with cells expressing a marker of lymphatic and precursor endothelium. Using a catalyzed signal amplification method without PCR, Reed et al. demonstrated that viral cyclin D was expressed in the latently infected portion of lesional spindle cells and that the number of staining cells increased with KS progression (418). Viral cyclin D expression was also detected in keratinocytes, eccrine epithelium, and the endothelium of the perilesional dermis (418).

HIV-1 in KS Histopathogenesis

Whether KS is a true malignancy, a reactive proliferation, or both remains unclear. Thus, early KS seems to be a reactive process of polyclonal nature, whereas it may progress in time into a true sarcoma (154). The aggressiveness of AIDS-associated KS implicates infection with HIV-1 as a necessary cofactor in rapid KS progression; indeed, the time of KSHV seroconversion until the onset of KS may be decades in classic KS (78, 268), while it is estimated at 2 to 10 years in AIDS-associated KS (175, 325, 425). In dually infected individuals, a local and systemic increase in the level of Th1-type cytokines seems to activate KSHV infection, resulting in increased viral load, antibody titers, expanded cell tropism, and KS (488).

The HIV-1 Tat protein has been directly implicated in the development of AIDS-associated KS. Tat induces KS-like lesions when overexpressed alone in transgenic mice (518) and synergizes when coinjected with bFGF in nude mice (152). Ex vivo studies demonstrate that extracellular Tat stimulates monocyte-derived macrophages to secrete IL-8 and Groα, two chemokines that are potently proangiogenic for endothelial cells (284). Extracellular Tat also can sustain AIDS-associated KS cell growth and survival (8, 32, 151) and exerts a biphasic antiapoptotic effect on KS cells by (i) global induction of anti apoptotic gene expression and (ii) activation of Akt kinase activity (128). These functions of Tat are mediated by direct interactions with VEGF receptor 2 (VEGFR-2) and insulin-like growth factor (IGF) receptor I (128). Similarly, integrin binding by extracellular Tat is responsible for many of its proliferative and proangiogenic functions (reviewed in reference 511). KSHV virions also utilize integrins as receptors and activate downstream signaling after binding target cells (4; also see below), similar to other herpesviruses (464, 544). Therefore, the interaction of both extracellular Tat and KSHV virions with integrins might represent a common mechanism for priming a target cell physiologically for subsequent viral infection and pathogenic exacerbation.

HIV-1 also has direct effects on KSHV. Conditioned media from T cells infected by HIV-1 induces lytic reactivation of KSHV in PEL cells (339), as does replication of HIV-1 in PEL cells (510). HIV-1 Tat and Vpr proteins can induce KSHV gene expression, and, reciprocally, the lytic switch protein of KSHV can synergize with Tat in activating the HIV-1 long terminal repeat (LTR) (224).

TISSUE CULTURE MODELS OF ENDOTHELIAL KSHV INFECTION

Critical proof of the transforming potential of KSHV came from de novo infection of cultured bone marrow microvascular endothelial cells and HUVECs. KSHV infection conferred long-term survival of both cell types, and anchorage-independent growth of the HUVECs (159). However, after long-term passage, only 5% of HUVECs maintained KSHV DNA; unlike primary cultures, the uninfected cells retained the ability to respond to VEGF, suggesting that their survival was dependent on paracrine VEGF provided by the infected cells of the population (159). However, serial passage of telomerase-immortalized microvascular endothelial cells infected de novo by KSHV leads to complete loss of virus, similar to spindle cells explanted from KS lesions, without growth transformation of the cells (278). KSHV infection of cultured primary human dermal microvascular endothelial cells (DMVECs) induces colonies of latently infected spindle-shaped cells and can be maintained only by diluting infected cultures into uninfected cells (106). The inability to passage latently infected cells suggested that the cultures were not transformed by KSHV (106); however, KSHV infection could enhance the transformed phenotype of DMVECs stably expressing the human papillomavirus E6 and E7 proteins prior to KSHV infection (358). Sakurada et al. demonstrated that induced PEL cells can very efficiently transmit KSHV directly to HUVECs in culture, highlighting the potential for direct cell-to-cell transmission of KSHV (441).

Primary endothelial cells isolated from (i) the dermis of human neonatal foreskin (fMVDEC) or adult breast and (ii) human uterine myometrium are all efficiently infected by purified KSHV (130). Cerimele et al. recently provided ex vivo confirmation of the detection of KSHV DNA in nonendothelial cells of KS lesions by demonstrating de novo infection of primary human keratinocytes (79). Like infection of primary HUVECs, the keratinocytes were transformed by KSHV but did not maintain the viral genome (79).

Purified KSHV virions bind readily to the surface of B cells and monocytes, but not T or NK cells, when mixed with peripheral blood specimens (130). Although the two cell types in which KSHV DNA is most consistently observed in vivo, endothelial cells and B lymphocytes, correspond to the sites associated most strongly with KSHV pathogenesis, the virus exhibits a very broad host range in tissue culture (44, 79, 106, 159, 163, 358, 422, 514). By analogy to many other herpesviruses, recent studies have demonstrated that heparan sulfate, a ubiquitous cell surface molecule, can serve as a receptor for KSHV, specifically interacting with the KSHV virion proteins K8.1 and glycoprotein B (gB) (3, 5, 42, 521). A more restricted cell surface protein, $\alpha_3\beta_1$-integrin, also functions as a KSHV receptor on human foreskin fibroblasts and human DMVECs through interactions with gB (4). Independent cell surface expression of gB, gH, and gL can mediate cell fusion between heterologous, uninfected cells, suggesting that this model recreates both binding and postbinding functions in entry of KSHV (400). However, similar to some endothelial models of infection, virtually all cultured cells tested do not support "one-step," productive viral infection, nor are they permissive for latent KSHV infection. Providing one potential explanation for this shortfall, Friborg et al. have shown that 293 cells support efficient replication of KSHV derived from KS lesions but not from BCBL-1 (PEL) cells (166). Thus, the tropism of KSHV depends only partly on successful entry of host cells; considering that clinical infection by herpesviruses leads to lifelong viral persistence, postentry events that support the establishment and maintenance of latency are critical for KSHV pathogenesis.

De novo models of KSHV infection suggest a complex pattern of viral gene expression and replication following entry. In fMVDEC, steady-state levels of two viral lytic RNAs (nut-1/pan and K8.1) increased linearly after infection until the cells were reductively divided, but that of the viral G-protein-coupled receptor (vGPCR) cycled with a 48- to 72-h periodicity, suggesting a dynamic, synchronous infection (130). Analyses of

viral gene expression and detection of both closed circular (i.e., latent episomes) and linear (lytic) genomic viral DNA suggested that both lytic and latent replication were occurring simultaneously in the infected-cell population (130), but the relationship of this provocative observation to the multiplicity of infection it is not known.

De novo infection of cultured endothelial cells has also provided a critical starting point to evaluate postentry effects of KSHV on host cell gene expression and physiology. Global microarray studies of latently infected DMVECs have demonstrated a significant upregulation of transcripts from IFN-induced genes (especially interferon response factor 7 [IRF-7]), proinflammatory genes (such as MCP-1, GPCR kinases, CD36, and RDC1), genes involved in cell division (including CDC25B), and tumorigenic genes (c-*jun, junD,* c-*kit,* c-*mer,* and others) (359, 406). Many inhibitors of the above cellular processes are also down-regulated by infection (359, 406). The c-*kit* inhibitor STI 571 (Gleevec) inhibits the proliferation of KSHV-infected DMVECs in response to the c-*kit* ligand, scatter factor, and a dominant negative mutant of c-*kit* reverses the transformation of DMVECs by KSHV infection (359). Independent overexpression of c-*kit* in uninfected DMVECs induces their morphologic conversion to spindle cells, suggesting that induction of c-*kit* expression by KSHV infection contributes to the ability of the virus to engender endothelial growth deregulation (359).

In particular, KSHV infection of cultured endothelial cells induces a complex response of the expression and function of angiogenic genes that seems to be influenced not only by the pretransformed status of the cells but also by the uniformity of infection. In HUVECs that are immortalized by KSHV infection but maintain the virus in only 1 to 5% of cells, VEGF, VEGF-C, VEGF-D, placental growth factor, and VEGFR-1 through VEGFR-3 were all induced relative to the situation in uninfected cells (327). Furthermore, treatment of the infected cells with VEGFR-2-neutralizing antibody or VEGF antisense oligonucleotides impaired their growth. A uniform, latent KSHV infection of HPV E6/E7-immortalized DMVECs also induced VEGFR-2 (359); however, infection of primary DMVECs by KSHV had no effect on any VEGF cytokines or receptors (406). Similarly, neutralizing antibodies to VEGF failed to inhibit angiogenesis stimulated by KSHV-infected DMVECs implanted in SCID mice or chemotaxis of endothelial cells induced by the infected cells in vitro (284). Instead, this study showed that IL-8 and GROα were the KSHV-induced mediators of these effects. Prior transformation of DMVECs also may be responsible for blunting of the induction of the IFN pathway in response to KSHV infection (359).

Treatment of KSHV-infected primary DMVECs with TPA (12-*O*-tetradecanoylphorbol-13-acetate) allowed an analysis of effects of the KSHV lytic cycle on endothelial gene expression (406). Many, but not all, of the induced genes were those that were up-regulated by infection in the absence of TPA; they included 10 IFN pathway genes, IRF-7, STAT1, and IGF binding protein 1 (IGFP-1). A set of genes with the potential for both complementary and antagonistic function to the induced genes were down-regulated after TPA treatment. Finally, an interesting observation was that many genes induced by infection of DMVECs with KSHV were regulated similarly to treatment of uninfected DMVECS with TPA.

KS spindle cells that have lost the virus after ex vivo culture have provided an interesting paradigm for understanding the high ratio of male to female KS cases in humans. Implanted in nude mice, these cells grew more rapidly and formed larger tumors in males than in females (9). In female mice, tumor development was inhibited during early pregnancy when a chorionic gonadotropin (CG)-like activity is high, and crude preparations of human CG (hCG) caused regression of tumors and inhibition of focus formation of these cells (314) by inducing apoptosis (442). Further purification of hCG preparations demonstrated that the anti-KS activity could be separated from the hCG molecule and resided in an RNase called eosinophil-derived neurotoxin (EDN) (199, 200, 313). Recombinant EDN had potent, cancer-specific, cytotoxic effects on KS cells if it contained the four proximal amino acids of its cognate signal peptide but not if it was without them (373). Treatment of humans with crude hCG preparations confirmed its clinical efficacy, leading to regression of cutaneous and visceral KS lesions (181, 218).

KSHV INFECTION IN ANIMAL MODELS

The transplantion of human tissue to mice with severe combined immunodeficiency disease (SCID/hu mice) not only has provided valuable models for KSHV pathogenesis but also has demonstrated the strict species barrier for infection by the virus. Injection of infected PEL (BCBL-1) cells into SCID mice evoked MCD-like immunoblastic lymphomas that were prominently neovascularized by murine-derived cells; the murine cells, nonetheless, remained uninfected (401). Although peritoneal tumors and ascites were produced, only subcutaneous and not intraperitoneal (i.p.), injection of the PELs led to dissemination of the lymphomas. The majority of tumor cells in this model remained latently infected by KSHV, and the virus could not infect coinjected human PBMCs even if the PELs were pretreated with TPA to induce reactivation.

A similar approach using nonobese diabetic (NOD)/SCID mice revealed a significant pathogenic difference resulting from injection of PEL cell lines that were either singly ($KSHV^+$) or dually ($KSHV^+/EBV^+$) infected. PEL-like effusions were produced following i.p. injection of both types of PEL cells, whereas only the dually infected, but not monoinfected, PEL produced an effusion following intravenous injection (51). These authors demonstrated that 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. The dually infected PELs expressed adhesion molecules that were very similar to EBV-positive Burkitt's lymphoma cells, suggesting an explanation for the differential metastasis to solid tumors (as in Burkitt's lymphoma) between the PEL types.

A third study suggested that PELs secrete VEGF to accelerate the vascular permeability of peritoneal vessels, leading to effusion rather than to neovascularization of tumors (21). 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.

De novo infection of SCID/hu mice by KSHV has been documented for transplanted fetal thymus and liver (thy/liv) (135),

and human skin grafted in keratome strips (162). The thy/liv model demonstrated a transient lytic and persistent latent infection of $CD19^+$ B cells that did not spread to mouse tissue, suggesting an appropriate model for initial infection and persistence of the virus in its authentic reservoir. In the skin model, six of eight mice developed KS-like lesions with angiogenesis. 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.

PHYSICAL AND GENETIC STRUCTURE OF KSHV

The coding capacity of the KSHV genome was determined by sequencing of viral DNA isolated from both a PEL cell line and biopsy specimens of KS (372, 436). Complementing this approach, Gardella gel analyses were used to demonstrate the size and conformation of the viral nucleic acid (423). Similar to the HVS and EBV genomes, the KSHV genome is maintained during latency in PEL cell lines as a circular, multicopy episome and contains multiple GC-rich, 801-bp terminal repeats (279) flanking approximately 145 kb of "unique" sequence (351) (Fig. 1). During productive replication, viral progeny DNA is ultimately synthesized as linear, single-unit genomes destined for incorporation into independent virions (423).

Purified virions released from PEL cells treated with TPA and sodium butyrate contain three types of capsid, named A, B, and C (371). Fully mature C capsids have a total mass of 300 MDa and, in declining order of abundance, contain the polypeptides ORF25/MCP (major capsid protein), ORF65/SCIP (small capsomer-interacting protein), ORF26/TRI-2 (triplex-2), ORF62/TRI-1, and the 160- to 170-kb (unique plus repeats) viral genome (371). A and B capsids contain the four proteins listed above but lack viral genomic DNA; B capsids contain, in addition, the scaffolding protein encoded by ORF17.5 (371). Cryoelectron microscopy at 24 Å resolution and digital reconstruction demonstrate that the capsid is icosahedral with a diameter of approximately 1,140 to 1,300 Å (504, 535). The characteristic herpesvirus tegument and envelope presumably are added to the capsids during egress.

KSHV contains at least 87 open reading frames (ORFs) (372, 436) (Fig. 1). Comparison of its genome with that of HVS (the prototype gammaherpesvirus) reveals a remarkably similar genetic organization (436). The two family members share 68 conserved genes that are arranged colinearly, with short, interspersed regions of genes unique to each virus. Each conserved gene has been given the prefix "ORF" and numbered consecutively from left to right along the genome, while the unique genes have been designated K1 to K15 (436). The more recent publication of the complete genomic sequences of the rhesus rhadinovirus (10, 455) and murine gammaherpesvirus 68 (515) has confirmed and extended the conservation of this genetic organization to additional nonhuman gammaherpesviruses. The genes with highest conservation among these viruses are those predicted to perform metabolic and catalytic roles in viral DNA replication (or virion structure [463]) and are included in a set of "ancient" genes conserved in all mammalian herpesviruses (334). In KSHV, these include the DNA polymerase and processivity factor (ORF9 and ORF59, respectively), DNA helicase-primase (ORF40, ORF41, and ORF44), thymidylate synthase (ORF70), and thymidine kinase (ORF21). Conversely, many of the K genes are homologs of cellular growth control and signaling molecules (372, 436) and are postulated to have been "captured" from the human host genome over a wide coevolutionary window (Fig. 1) (334). The KSHV genome also contains two origins that support lytic replication of heterologous plasmids and are inverted duplications of each other: oriLyt-L lies between K4.2 and K5, and oriLyt-R lies between ORF69 and vFLIP (26) (Fig. 1).

These analyses have also revealed that the viral DNA polymerase gene has the highest intervirus identity, facilitating the construction of a densely branched rhadinoviral phylogenetic tree which includes KSHV, HVS, and nine additional primate rhadinoviruses that have been identified over the last half decade (197) (the rhadinovirus tree does not include EBV, the other human gammaherpesvirus). The rhadinoviruses have since been subdivided into those of New World and Old World primates; the Old World viruses, including KSHV, have been further subdivided into groups RV-1 and RV-2 (197). The branching order of the RV-1 group, which includes KSHV, follows that of the host species (197). Although not completely sequenced at the time of publication, *Pan troglodytes* (chimpanzee) rhadinovirus 1 is most probably the closest KSHV homolog, encoding a DNA polymerase gene that has 93.2% amino acid identity to the KSHV polymerase (198).

KSHV Subtypes and Geographic Variability

Although KSHV occupies a single branch within the dense phylogenetic tree of nonhuman rhadinoviruses, its nucleic acid displays significant intragenomic heterogeneity. In an attempt to uncover the molecular basis for the extreme pathogenic and epidemiologic variation in the different forms of KS, numerous groups have initiated a comprehensive, comparative sequence analysis of KSHV DNA from specimens from AIDS-associated, classic, and endemic KS patients worldwide. The earliest studies revealed that the ORF25/26 and ORF75 loci of different isolates displayed approximately 1.5% sequence divergence (407, 553). Although small, these differences were significant enough to divide individual isolates into subgroups A, B, C, and N with intertypic recombination (6, 407, 553). However, as predicted by the original full-length sequence comparisons within the gammaherpesviruses, it was later discovered that the genomic variability is not evenly distributed within the virus; instead, individual genes are evolving at different rates (215, 334). In fact, the greatest sequence divergence is not in ORF25/26 and ORF75 but is concentrated within the K1 locus at the extreme left side of the genome (551, 552) (Fig. 1).

The amino acid sequence of K1 differs by 0.4 to 44% between KSHV isolates and has permitted further differentiation of the virus into six subtypes in multiple studies (A, B, C, D, E, and Z, with more than 24 clades [41, 215, 242, 246, 551, 552]). These data support an extremely strong linkage of the KSHV subtype to the geographic origin of the infected host. Subtypes A and C are most similar and prevail in Europe, the United States, and northern Asia (551). Subtypes B and A5 are characteristic for Africa (242, 551), and subtype D is found in the countries from the Pacific Islands region (551). Subtype E has more recently been identified in Brazilian Amerindians (41),

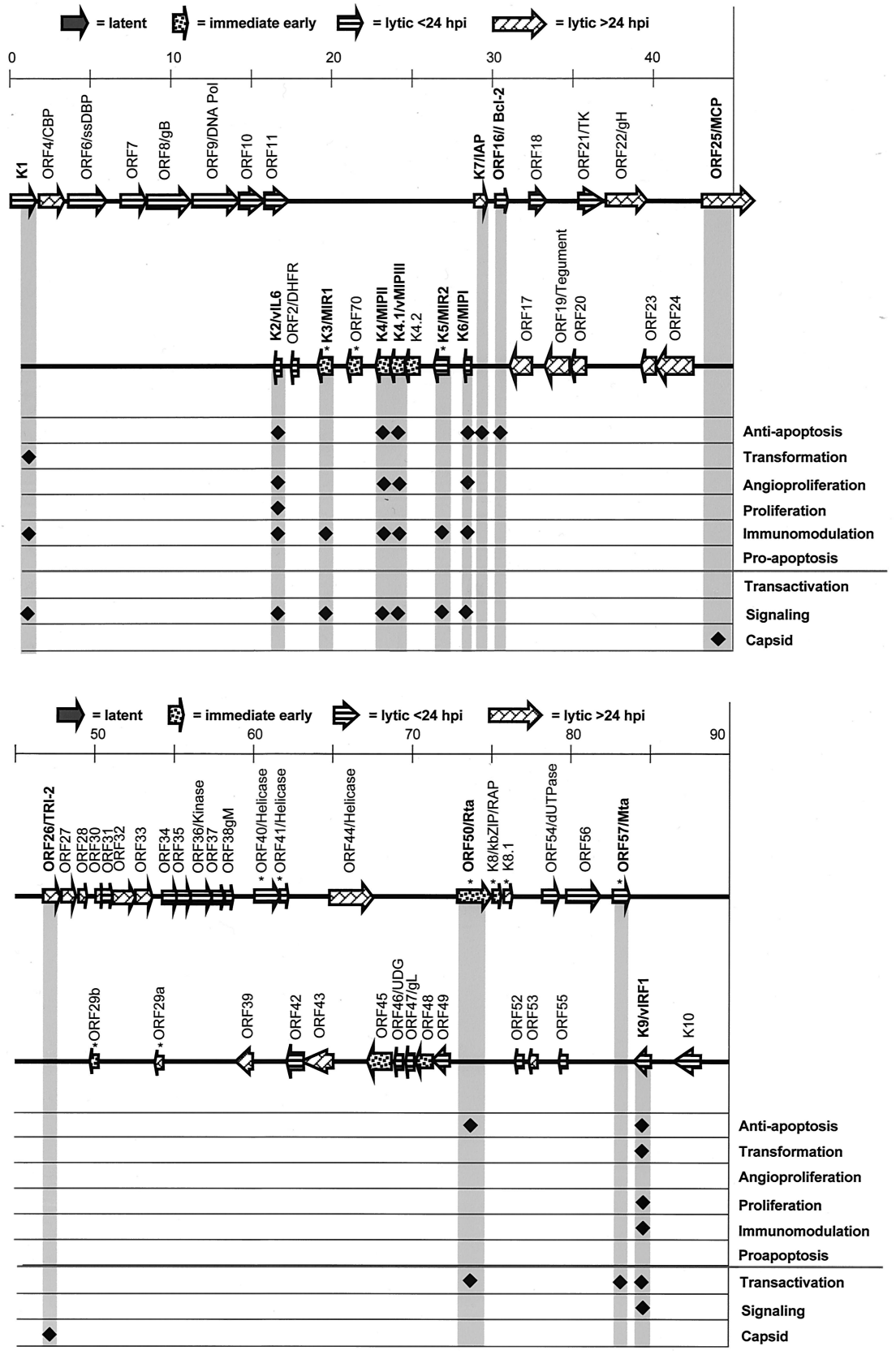
= latent
= immediate early
= lytic <24 hpi
= lytic >24 hpi
0
10
20
30
40
K1
ORF4/CBP
ORF6/ssDBP
ORF7
ORF8/gB
ORF9/DNA Pol
ORF10
ORF11
K7/IAP
ORF16// Bcl-2
ORF18
ORF21/TK
ORF22/gH
ORF25/MCP
K2/vIL6
ORF2/DHFR
K3/MIR1
ORF70
K4/MIPII
K4.1/vMIPIII
K4.2
K5/MIR2
K6/MIPI
ORF17
ORF19/Tegument
ORF20
ORF23
ORF24
Anti-apoptosis
Transformation
Angioproliferation
Proliferation
Immunomodulation
Pro-apoptosis
Transactivation
Signaling
Capsid
= latent
= immediate early
= lytic <24 hpi
= lytic >24 hpi
50
60
70
80
90
ORF26/TRI-2
ORF27
ORF28
ORF30
ORF31
ORF32
ORF33
ORF34
ORF35
ORF36/Kinase
ORF37
ORF38gM
ORF40/Helicase
ORF41/Helicase
ORF44/Helicase
ORF50/Rta
K8/kbZIP/RAP
K8.1
ORF54/dUTPase
ORF56
ORF57/Mta
ORF29b
ORF29a
ORF39
ORF42
ORF43
ORF45
ORF46/UDG
ORF47/gL
ORF48
ORF49
ORF52
ORF53
ORF55
K9/vIRF1
K10
Anti-apoptosis
Transformation
Angioproliferation
Proliferation
Immunomodulation
Proapoptosis
Transactivation
Signaling
Capsid

FIG. 1

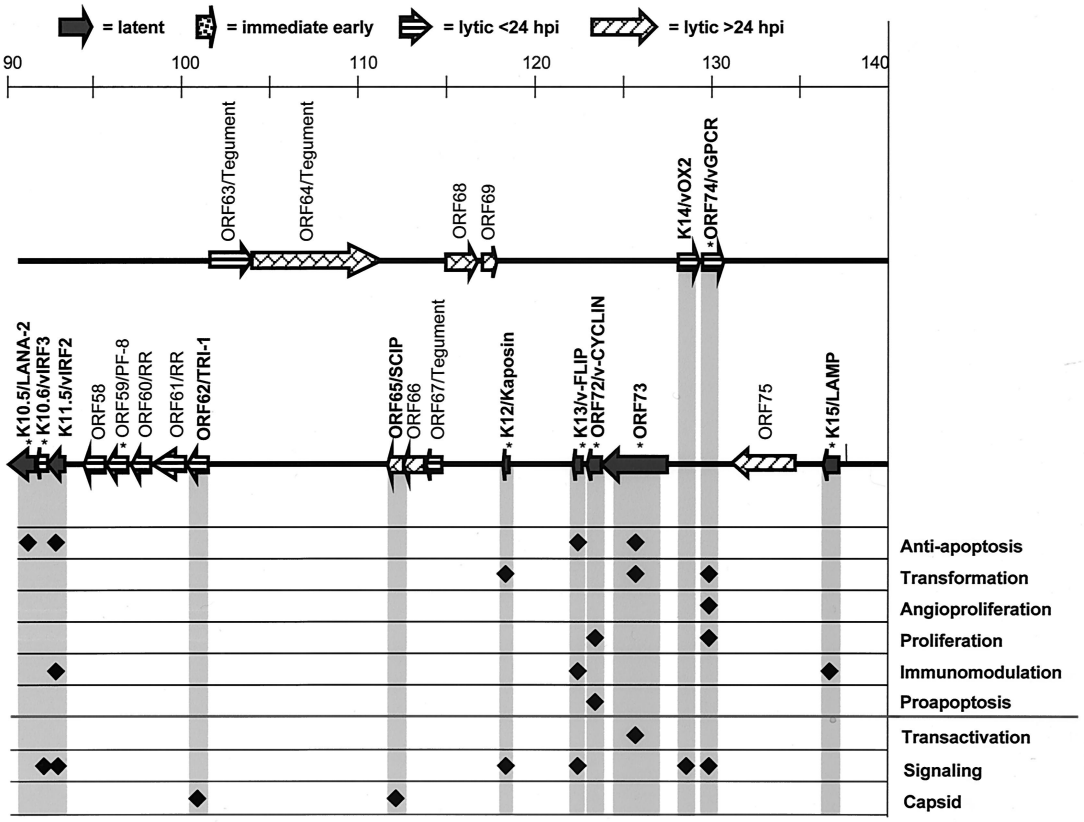

FIG. 1. ORF map of the KSHV genome. A linear representation of the KSHV genome, showing the position of the ORFs as published in references 63, 309, 351, 431, 436 is shown. Each ORF is represented by an arrow pointing in the direction in which it is expressed; ORFs are displayed linearly in two groups based on leftward or rightward direction. Approximate nucleotide positions are indicated in kilobases in the scale at top, as in reference 436. The expression kinetics of each ORF in PEL models of latency and reactivation are indicated by the fill of each arrow, as shown in the figure: latent (65, 122, 134, 156, 184, 431, 444, 483), IE (430, 448, 487, 489, 542), and lytic <24 h postinduction (hpi) and >24 h postinduction (236, 393) are all shown. An asterisk above an ORF indicates that at least one transcript encoding the ORF is spliced (either removing part of the ORF or introducing additional exons from outside the ORF). ORFs with published functions are indicated by bold lettering, and their respective functions are shown (see the text for relevant references). The nomenclature of each ORF follows that of reference 436 and other references in the text. CBP, complement binding protein; DHFR, dihydrofolate reductase; TK, thymidine kinase; PF, processivity factor; UDG, uracil-DNA glycosylase; RR, ribonucleotide reductase; other abbreviations are defined in the text.

and subtype Z has been found in a small cohort of Zambian children (246). Conclusive evidence of the geographic association of genotype comes from studies of infected emigrants, who harbor virus subtypes characteristic of their countries of origin but not their adopted homes (551). Strain analysis of the viruses responsible for 15 KS cases in ethnically diverse eastern Taiwan showed the rarely described strain D in four aborigines and strain C more common among Han Chinese KS patients (222); furthermore, two isolates obtained from African immigrants to the United States were B subtype virus, not the prevailing U.S. forms (551). Among classic KS patients of Ashkenazi origin in Israel, strain A1 predominates, whereas among North African Sephardic Jews, C2 and C6 variants prevail instead (551).

The mutation rates in K1 approximate those in genes in other human pathogens (for instance, HIV-1 *env*), but there is no evidence for a herpesvirus error-prone replication mechanism that would permit rapid positive selection of the K1 gene (215, 433). Furthermore, isolation of multiple K1 subtype viruses from a single individual is not universal. A comparison of PEL specimens and anatomically distinct KS lesions taken over time from nine individuals harbored identical viruses (551, 552), suggesting that K1 variation does not occur over the lifetime of a single infected host. However, K1 genes isolated from biopsy specimens obtained 4 months apart in Russian patients had acquired up to 5 nucleotide and amino acid changes in four of the seven patients (276). Although these current PCR-based genotyping methods have suggested that infection by a single KSHV variant predominates, and may be exclusive, in many individuals, isolation of recombinant genomes argues strongly that coincident infection of a single host by different KSHV subtypes must occur. A population that might be investigated to address the issue of viral evolution is KSHV-positive Zambian children presenting with either febrile illness (i.e., no KS) or childhood endemic KS (246). In one study, all 13 children harbored the rare Z variant of K1, regardless of concomitant KS or HIV seropositivity; due to their young age, these variants probably represented primary infections. A prospective analysis of strain status and progress of infection would be highly informative; of course, a potential complication would be multiple exposures to variant viruses. Nonetheless, this may confirm the superinfection/coinfection hypothesis.

Adding to the divergence at the K1 locus is the observation that the K15 gene, from the extreme right side of the viral genome (Fig. 1), exists as two distinct alleles. The M and P (for "minor" and "predominant") alleles of K15 are 67% divergent (407). Although the overall divergence within each allele approximates the natural variation found in most of the KSHV genome, four isolates with K15 alleles that have diverged further have been described (242) or postulated (551). Like K1, the K15 alleles are geographically delimited and are partially linked to particular K1 subtypes. The M K15 allele was identified in 14 of 49 West and Central, but not East, African samples by Lacoste et al. (275); however, it was not detected among 21 African KSHV specimens by Zong et al (with the exception of three U.S. AIDS patients with West African heritage) (551). In a small Russian cohort, four of seven samples harbored virus with M alleles (276). It has been postulated that the M K15 alleles are derived from a novel, possibly nonhuman, rhadinovirus by ancient recombination events and that the M allele may be evolving toward a higher prevalence in the population (551). Linkage analyses have shown that up to 20 kb, including "M alleles" of eight neighboring genes, is frequently linked to the M K15 allele, suggesting a generous transfer of genetic information from the M virus (551).

The proteins encoded by the K1 and K15 genes are attractive candidates for playing a direct role in KSHV pathogenesis. K1 and K15 are positional homologs of transforming genes in EBV and HVS (215), and K1 can functionally replace its homolog in transformation of lymphoid cells by HVS (289). Mice transgenic for K1 develop KS-like tumors and plasmablastic lymphomas in which there is constitutive activation of NF-κB, Oct-2, and Lyn (408). K1 may also assist immune evasion of infected cells by its ability to inhibit transport of B-cell receptor complexes to the surface of B cells (286). The K1 product is a transmembrane protein localized to the cell surface that signals constitutively through its cytoplasmic immunoreceptor tyrosine activation motif (ITAM), activating the well-characterized cellular nuclear factor of activated transcription (NFAT) growth control pathway (281, 288). This function of K1 is critical for KSHV replication, since truncation of the ITAM creates a mutant K1 that represses viral replication following reactivation from latency, in a dominant negative fashion (280). Furthermore, the ITAM is conserved in all diverged variants of K1 (41, 246, 551, 552). Additional studies demonstrated that overexpression of wild-type K1 can also inhibit TPA induction of viral reactivation in PELs without altering the expression of the viral lytic switch protein; this occurs by inhibition of cellular AP-1, NF-κB, and Oct-1 activity, suggesting that K1 may help fine-tune viral gene expression to modulate KSHV reactivation (287).

The K15 gene encodes a latently expressed protein with a cytoplasmic domain that contains SH2 motifs, interacts with TRAF (tumor necrosis factor receptor-associated factor) and antiapoptotic proteins, and represses B-cell receptor signaling (101, 184, 460). The M and P forms of K15 conserve a similar splicing structure and two C-terminal SH2 domains (407).

However, whether a particular viral genotype can be connected to (i) development or progression of KS (or any of the other KSHV-associated diseases) or (ii) a particular clinicoepidemiologic form of KS remains an open question. Genotyping of numerous, geographically distinct AIDS populations has shown no clear correlation between a particular K1 or K15 variant and pathogenesis of KS, PEL, or MCD (215, 222, 242, 275, 551). A recent case report demonstrated that KSHV isolated from individual KS, PEL, and MCD specimens from the same patient all had the identical K1 genotype (484). Likewise, classic KS in Italy correlates geographically with KSHV seroprevalence rather than KSHV subtype (109). In France, a genotyping study of only ORF26 demonstrated that subtype A was isolated from the more aggressive forms of KS, but the viral genotype was incomplete, since linkage of ORF26 to other loci was not evaluated (48).

Nevertheless, studies of populations in which seroprevalence is high but KS incidence is low have affirmed a role for both virus and host genotype in disease phenotype. Most of sub-Saharan Africa experiences a high KSHV seroprevalence, with the B subtype predominating throughout, yet endemic KS is confined primarily to East and Central Africa and variably in West Africa (275). Conversely, a population of 781 Brazilian Amerindians who have a 53% KSHV seroprevalence but a 0% KS incidence are infected with a rare K1 E subtype virus, while other South American isolates are A or C subtypes (the authors concede, however, that reporting of KS in Amerindians may be incomplete). The molecular basis of host susceptibility to KS has been virtually unexplored (319); however, sex-specific discrepancies in KS incidence (188, 251, 532) might be partially explained by hormonal factors (54, 313) (see discussion, above).

Heterogeneity within the ORF73 gene, which encodes the pathognomic, seroepidemiologic target antigen LANA-1 (discussed above), has independently been utilized to genotype individual viral isolates. In the prototype BC-1 virus, the ORF73 gene contains a 3,489-nucleotide (nt) ORF that includes an internal repeat domain (IRD) within nt 929 to 2826 (538) (Fig. 2). The IRD itself can be further subdivided into three repeat regions, with the outer two encoding mostly acidic amino acids and the inner one encoding a preponderance of glutamine residues. The ORF73 IRD is highly variable among individual KSHV isolates, with variations due to insertions, deletions, and point mutations but never frameshifts or nonsense codons (538). As a result, LANA-1 from different isolates contains variable numbers of acidic repeats, with the glutamine-rich region (region II), in particular, being a hot spot for amino acid variation (177, 537).

Comparison of the respective electrophoretic mobilities of products of PCR amplification across the IRD provides a characteristic KVNAtype, or genotype, of individual viruses from distinct PEL cells and clinical specimens (177). Multiple specimens from single patients had the same KVNAtype, although two KS specimens showed evidence of a minor, second KVNA type. Furthermore, various PEL cell lines carry latent virus with unique KVNAtypes (177). Combining this PCR approach with restriction digestion at sites within the IRD (i.e., PCR plus restriction fragment length polymorphism), allowed even higher resolution of individual viral genotypes (538). This approach confirmed that there is little or no variation in viral genotype in multiple KS lesions from the same patients and demonstrated that variability in the IRD is independent of both the ORF26 (538) and K1 (110) genotypes. PCR plus restriction fragment length polymorphism of ORF73 has more recently been used to track inter- and intrafamilial transmis-

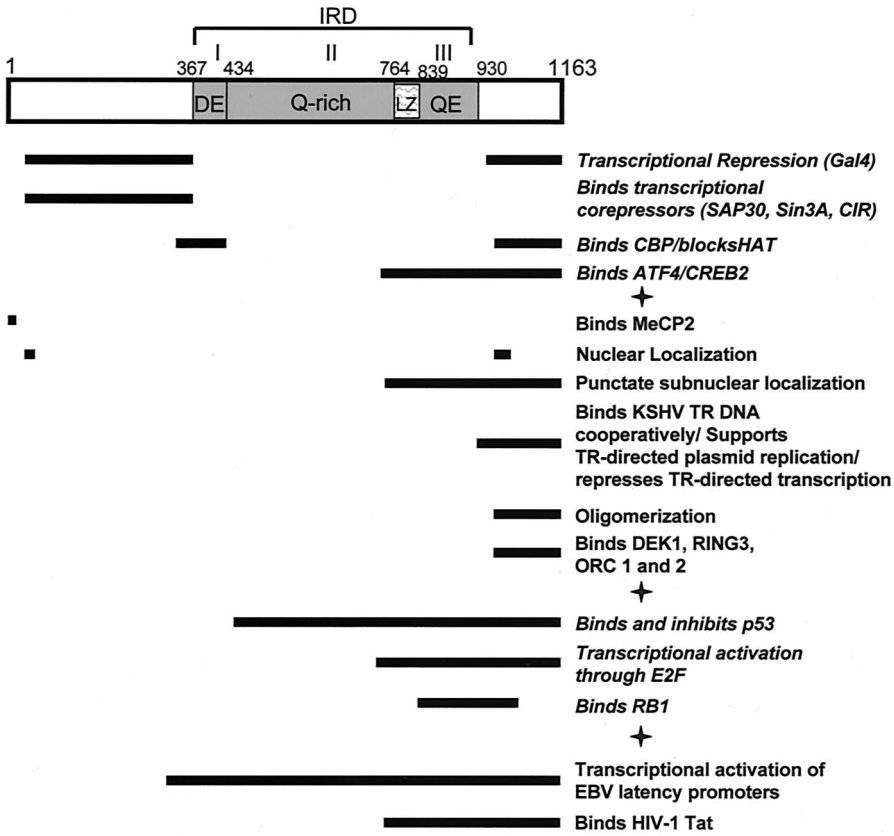

FIG. 2. Primary structure-function map of KSHV ORF73/LANA-1. This schematic shows a linear representation of the amino acid content and predicted structural motifs of the LANA-1 protein. The amino acid numbering is as published in reference 436 and corresponds to the virus from BC-1 cells. The internal repeat domain (IRD) is shown by the bracket, as in reference 538, and is described in the text. The approximate position of each functional domain is shown by a black bar, corresponding to the function shown in the column on the right (see the text for references). No amino acid boundaries are indicated for the functional domains, since functional mapping has used different isolates of LANA-1 that are variable in size. Abbreviations: DE, aspartic acid/glutamic acid rich; Q, glutamine, LZ, putative leucine zipper; QE, glutamine/glutamic acid rich.

sion of virus isolated from both mouth rinses and peripheral blood of Malawian KS patients (110).

The IRD may be a crucial domain for mediating protein-protein interactions of the cognate LANA-1 protein in transcriptional regulation of both viral and cellular genes. Although mutational studies have suggested that the role of LANA-1 in maintenance of the latent KSHV episome is independent of the intact IRD (178, 179, 223) (discussed below), most truncated derivatives of LANA-1 that retain both positive and negative transcriptional effects include all or part of the IRD (Fig. 1). Transcriptional activation by LANA-1 is probably independent of direct DNA binding, since LANA activates transcription directed by a wide array of simple, synthetic promoters containing binding sites for the cellular proteins ATF, AP-1, CAAT, or Sp1, linked to a TATA box (421). Although the TATA box alone was also activated by LANA-1 in these studies (421), activation of the cellular IL-6 promoter by LANA requires both a TATA box and an upstream AP-1 element (15), and activation of the HIV-1 LTR in BJAB cells requires both the TATA box and the core enhancer elements (NF–IL-6, Ets, NF-κB, and Sp1 sites) (227). However, LANA-1 can activate the HIV-1 LTR independently of the core enhancer if the Tat protein is coexpressed; this effect is mediated by the carboxy-terminal 400 amino acids (aa) of LANA-1, which includes the third repeat region (227). Truncated LANA-1 containing the IRD plus the C terminus activates the transcription of an EBV latency promoter containing PU.1, ATF, and Sp1 elements (202). Mechanistically, LANA-1 can modify the DNA binding activity of Sp1 to activate the transcription of the telomerase reverse transcriptase promoter (265). Finally, similar to the oncogenes of small DNA tumor viruses, a LANA-1 truncation containing aa 803 to 990 (including the third repeat region [Fig. 2]) binds to the pocket domain of RB1 to facilitate E2F-dependent activation of the cyclin E promoter; this disruption of RB1 function suggests one mechanism by which LANA-1 cooperates in cellular transformation with H-ras (415). Taken together, these studies suggest that LANA-1 activates transcription by undergoing promiscuous interactions with multiple cellular transcription factors; further structure-function studies of LANA-1 are necessary to determine the influence of the IRD in these interactions.

LANA-1, however, can also contribute to broad repressive effects on transcription. In Cos cells, LANA-1 represses the transcriptional activity of NF-κB, and repression of the HIV-1 LTR in this study (421) suggests that the interactions of LANA-1 with the cellular transcription apparatus is cell specific. LANA-1 also represses transcription controlled by the ATF4/CREB2 protein, independently of ATF4 DNA binding;

this effect is mediated by LANA-1 aa 751 to 1162, which includes the third repeat region (297) (Fig. 2). Similarly, the first acidic repeat (aa 340 to 431) of LANA-1 is one of two domains required to competitively bind the cellular cyclic AMP-responsive element binding protein (CREB) binding protein (CBP) and block its histone acetyltransferase activity, thus inhibiting the ability of CBP to coactivate transcription with c-fos (296). This mechanism might reflect the general ability of LANA-1 to repress transcription driven by other cellular and viral CBP-dependent transactivators, including the KSHV lytic switch protein ORF50/Rta (208). The entire IRD and C terminus of LANA-1 also directly binds to the p53 tumor suppressor to inhibit transactivation as well as apoptosis (167) (since p53 can repress the promoter of LANA-1, the interaction between the two proteins may also result in derepression of transcription, to contribute to autoactivation by LANA-1 and maintenance of its expression during infection [238, 421]). Thus, it is provocative to speculate that IRD polymorphisms in ORF73 (177, 538) might influence heterooligomerization of LANA-1 in a KVNAtype-specific manner, to tune the cell-specific, positive and negative interactions of LANA-1 with the cellular transcriptional machinery, resulting in variable consequences for viral replication and pathogenesis.

A final divergent locus that has not yet been evaluated for viral classification surrounds the K12 ORF (Fig. 1), which encodes the transforming protein kaposin (263, 291, 362, 363, 437). Different KSHV isolates derived from PELs or KS tissue demonstrate variable numbers of direct repeats of genomic sequence upstream of K12 (437). The repeats preserve all three respective ORFs and are transcribed in infection, encoding proteins containing variable numbers of peptide repeats with unknown function (discussed in more detail below) (437).

LATENT VERSUS LYTIC GENE EXPRESSION IN KSHV

Analagous to the other herpesviruses, KSHV exhibits both latent (nonproductive) and lytic (productive) replication, both of which are characterized by virtually distinct gene expression programs. This biphasic life cycle of KSHV was recognized early in both KS lesions (483) and cultured PEL specimens (342, 343, 424, 540). Productive infection by herpesviruses leads to cell lysis and death and obviously is not consistent with the ability of an infecting virus to transform its host cell. Therefore, classifying the latent or lytic cycle expression of individual KSHV ORFs is critical for predicting their potential roles in pathogenesis of the viral infection.

Assigning the expression of KSHV genes to the latent or lytic phase has benefited immensely from the ease of culturing PEL cells latently infected with KSHV and inducing lytic reactivation with common laboratory chemicals (such as phorbol esters or sodium butyrate). Individual PEL cell lines carry 40 to 150 copies of KSHV DNA per cell genome, respectively, with every cell in the culture infected (reviewed in reference 138). In normal passage of the cells, the virus is maintained as a latent episome, with highly restricted viral gene expression and lack of virus production. On chemical induction, viral gene expression switches from the latent program to an ordered cascade of lytic gene expression, leading to viral replication, virion production, cell lysis, and viral release (423, 424, 444, 540).

However, the differentiation of a viral gene as latent or lytic strictly by analysis of RNA expressed in bulk PEL cultures has been complicated by the characteristic small percentage of every cultured PEL population that experiences spontaneous lytic reactivation (424, 540). One powerful approach to overcome this problem is by analyzing KSHV gene expression at the single-cell level by ISH. When ISH was performed with KS specimens, the kaposin gene (K12) was expressed in at least 85% of spindle cells while the ORF25/MCP, a lytic structural protein in PELs (371) (and conserved across the *Herpesviridae*), was expressed in no more than 10% of the spindle cells (483). Kaposin was thus classified as a latent gene (483), and this approach provided a seminal paradigm for classifying expression of other KSHV genes.

Further genome-wide analyses of KSHV gene expression have also utilized PEL models of infection. The first such study compared the respective expression patterns of each viral ORF during normal culture of PELs (i.e., latency) to the response of each to TPA treatment and lytic viral induction (444). Each viral gene was thus distinguished as class I (constitutively expressed regardless of TPA treatment), class II (expressed without TPA and further induced by TPA addition), or class III (undetectable without TPA but induced by the chemical), respectively (444). This study revealed a cluster of three class I genes that included LANA-1, ORF72 (viral cyclin D [vCyc]), and K13 (fas-ligand IL-1 β-converting enzyme inhibitory protein [vFLIP]) (Fig. 1); their wide expression in KS specimens confirmed their latent classification (122, 134). The class III genes, in contrast, encoded mostly the viral structural and replication genes (typically late [L] genes in herpesviruses); the identification of kaposin as a class III gene in these cells (444), however, demonstrates that not all latent genes (437, 483) are class I. The class II genes consisted of typical herpesvirus regulatory and viral DNA replicative genes, as well as the majority of the viral homologs of cellular genes (discussed below) (444). More recent studies using DNA microarrays have permitted simultaneous comparisons of the transcription kinetics of virtually all the KSHV genes (236, 393). While confirming the original PEL-based classifications of the viral genes based on the addition of TPA, microarrays have demonstrated a powerful means of determining the kinetics of first appearance and peak expression of the lytic genes. For example, the peak expression of some candidate structural genes, such as ORF8/gB and ORF47/gL, occurs at early (12 h), rather than late (24 h) times, postinduction (393) (Fig. 1).

These genome-wide analyses of KSHV gene expression kinetics in PEL cells have complemented many individual studies of single viral genes or loci; two additional genes identified as latent, K10.5/LANA-2 and K11.5, encode homologs of IRFs (65, 431), and a third (expressed from K15) encodes the latency- associated membrane protein (LAMP) (184) (Fig. 1). Additional studies of gene expression following reactivation of latent virus have demonstrated that, typical of regulatory genes of herpesviruses, immediate early (IE, or α) transcripts could be identified based on their resistance to treatment of the PELs with cycloheximide (CHX); six IE loci with multiple transcripts (discussed below) have thus been identified, containing (Fig. 1) (i) ORF50 (replication and transcriptional activator [Rta]), K8, and K8.2 (K-basic-leucine zipper (bZIP)/replication-associated protein [RAP]), (ii) ORF45, (iii) K4.2,

K4.1, and K4 (vMIPs), (iv) ORF48 and ORF29b, (v) K3 and ORF70, and (vi) a transcript with no apparent coding potential (489, 490, 542). Similarly, typical of structural genes of herpesviruses, late (L, or γ) genes have been identified by their sensitivity to inhibitors of viral DNA replication, for example the ORF17 viral assembly protein (AP)/protease (Pr) and K8.1, a glycoprotein (87, 508). Studies of transcript architecture from individual loci have also demonstrated that numerous KSHV transcripts are spliced (Fig. 1), a gene expression strategy that is not axiomatic in the *Herpesviridae,* and many are polycistronic.

Remarkably, the low level of spontaneous lytic gene expression detected against the backdrop of latent expression in most PEL cultures (156, 236, 393, 444) is extremely similar to what is detected in KS clinical samples. Indeed, most infected cells in KS specimens display latent KSHV gene expression, with occasional cells expressing lytic transcripts (86, 143, 249, 301, 384, 389, 483, 489), suggesting that the low level of spontaneous lytic gene expression is not an artifact of tissue culture models. More recent models of de novo infection of cultured endothelial cells have also demonstrated a similar mixed pattern of gene expression (106, 278, 358).

Latent Genes and KSHV Pathogenesis

Similar to the latent expression of genes required for EBV transformation of primary B lymphocytes (reviewed in reference 256), KSHV expresses seven latent genes with demonstrated modulatory effects on host cell growth (Fig. 1); all are thus candidate effectors of KS pathogenesis.

The major latent locus: ORF73, ORF72, and K13. ORF73 (encoding LANA-1), ORF72 (v-cyclinD) and K13 (vFLICE) are all expressed from the same locus in polycistronic, differentially spliced mRNAs whose transcription is coordinately regulated by a common promoter (84, 134, 205, 447, 494). This promoter is bidirectional, controlling the constitutive expression of the latent genes to the left but lytic, TPA-inducible expression of the K14 and ORF74/vGPCR to the right (134, 238, 447, 494) (Fig. 1). LANA-1 can autoactivate transcription of the promoter in the latent direction (238, 421), and, similar to the human cyclin D1 promoter, the latent promoter is induced at the G_1-to-S transition of synchronized cells (447). In transgenic mice, the LANA-1 promoter is highly expressed in $CD19^+$ B cells, similar to its constitutive activity in PEL cells, but is not expressed in $CD3^+$ T cells (237). This tissue-specific activity of the LANA-1 promoter may thus help specify postentry persistence of KSHV in $CD19^+$ B cells of infected humans (13, 340).

As discussed above, LANA-1 (Fig. 2) both activates and represses transcription (15, 202, 227, 238, 265, 296, 421); it also subverts the tumor suppressors p53 and RB1, blocks apoptosis, and stimulates cellular transformation (167, 415). The observation that LANA-1 also associates with cellular chromatin (30, 115, 272, 273, 330, 402, 451, 492, 493) reflects the crucial role for this large protein in maintaining latent persistence of the viral episome. LANA-1 interacts directly with both components of host chromatin (Fig. 2), the protein (histone H1, DEK1, and RING3) (115, 272, 330, 404) and the DNA (31, 178, 179, 223, 298, 402, 493), to tether the viral episome to the host genome. In tissue culture cells expressing LANA-1, a single copy of one viral terminal repeat (TR) introduced into a heterologous plasmid is sufficient for its episomal maintenance (30, 31). The C-terminal 233 aa of LANA-1 binds as a sequence-specific dimer to two tandem 17-bp direct repeats found within each TR of the virus, with cooperative kinetics (31, 178, 179, 298, 451). The LANA-1 DNA binding site and an adjacent GC-rich region contained within a single TR together function as the putative origin of latent episomal replication when present on a plasmid; expression of the C-terminal DNA binding fragment of LANA-1 is sufficient to mediate this effect (178, 223), although the N-terminal 90 aa may also contribute (298). Reflecting its ability to bind the TR at the origin of replication, LANA-1 also interacts with the origin recognition complex 1 and 2 (Orc-1 and Orc-2) proteins (298).

LANA-1 also targets the protein component of chromatin, tying its role in viral replication to a role in transcriptional repression (Fig. 2). When placed upstream of a heterologous promoter, the TRs can function as transcriptional enhancers but are potently suppressed by the DNA binding domain of LANA-1 (178, 179, 298, 451). In fact, independent fusions of either the N or C terminus of LANA-1 to the Gal4 DNA binding domain can reproduce the transcriptional repression function of LANA-1 on heterologous promoters containing Gal4 binding sites (273, 451). The N-terminal repression domain binds directly to the transcriptional corepressor proteins SAP30, Sin3A, and CIR (273), while the C terminus binds to CBP (208). Cognate LANA-1 protein preferentially associates with heterochromatin and dominantly redistributes the cellular RING3 protein, a putative chromatin remodeling factor, from euchromatin to heterochromatin (330, 404, 493). Expression of the C-terminal domain in uninfected cells is sufficient to generate the characteristic punctate subnuclear localization of LANA-1 (402, 451) and also mediates binding to RING3 and DEK1, a second putative chromatin-remodeling factor (272, 404). However, the C-terminal domain is not sufficient to target LANA-1 to heterochromatin; instead, aa 1 to 15 of LANA-1 are tethered to heterochromatin through interactions with methyl-CpG binding protein 2 (MeCP-2) (272). Deletion of the N-terminal chromatin binding site abolishes the ability of LANA-1 to mediate episomal persistence, and can be rescued by fusion of the mutant protein to histone H1 but not histone H2B (462).

ORF72 encodes viral cyclin D (vCyc or kCyc) (Fig. 1), a protein that has 32% identity and 54% similarity to the cellular cyclin D2 (294). Like its cellular counterpart, vCyc forms functional complexes with cellular cyclin cdk6, phosphorylates RB1 and histone H1, and stimulates the G_1-to-S transition of the cell cycle (91, 185, 294, 491). However, the CDK inhibitors $p16^{Ink4a}$, $p21^{Cip1}$, and $p27^{Kip1}$, which limit the activity of the cellular cyclin-cdk complexes, are unable to block vCyc/cdk6 (491). For $p27^{Kip1}$ this difference is directly attributable to divergence of critical amino acids in the CDK inhibitor interface of vCyc that alter its conformation and prohibit a direct interaction between the proteins (71, 491). Furthermore, stimulation of cdk6 activity by vCyc does not require the cdk-activating kinase cycH/cdk7; however, complete resistance to p16, and efficient RB1 phosphorylation, do depend on cdk-activating kinase activation of vCyc/cdk6 (99, 243).

Viral cyclin also diverges from its cellular counterpart in having evolved a wider range of substrates as targets when

associated with cdk6. The phosphorylation of $p27^{Kip1}$ by vCyc/cdk6 leads to degradation of the CDK inhibitor by the cellular proteasome and is required for efficient stimulation of cell cycling by the vCyc (145, 320). The vCyc/cdk6 complex can also phosphorylate the cellular Bcl-2 protein, which leads to induction of apoptosis in cells expressing high levels of cdk6; interestingly, overexpression of the viral lytic cycle protein bcl-2 (ORF16), but not cellular bcl-2, can inhibit this effect (377, 378). Origin recognition complex 1 (ORC-1) protein is also a target of vCyc/cdk6 phosphorylation, which contributes to the ability of vCyc/cdk6 to stimulate cellular DNA replication even in the presence of the cdk inhibitor roscovotine (283). This raises the possibility that the latently expressed KSHV cyclin D not only stimulates cell cycling and replication of the host genome but also ensures replication of the latent viral genome.

K13 encodes the vFLIP protein (Fig. 1), which inhibits FADD-mediated apoptosis downstream of the Fas receptor (34, 136, 500). vFLIP blocks the protease activities of caspase-3, caspase-8, and caspase-9; it directly interacts with procaspase-8 to inhibit its activation (34, 136). Overexpression of vFLIP in Fas-sensitive, A20 B lymphoma cells allows their clonal outgrowth in the presence of Fas receptor activation and promotes tumor establishment and progression of A20 cells in immunocompetent mice, presumably by allowing evasion of CTL-mediated killing (136). vFLIP also constitutively activates the NF-κB pathway by direct interaction with the IκB kinase (IKK) complex in the cell cytosol (307), an activity that allows activation of the HIV-1 LTR (34). Inhibition of constitutive NF-κB activity in PEL cells induces programmed cell death (254); however, it is not clear whether vFLIP constitutively activates NF-κB for survival of infected endothelial cells.

K12/kaposin A. The 60-aa hydrophobic protein encoded by K12 (called kaposin A) (Fig. 1) transforms cultured cells and drives tumorigenesis when these cells are introduced into nude mice (263, 362, 363). Cells transformed by kaposin A show enhanced activation of numerous serine/threonine kinase pathways (363), increased adhesion to intercellular cell adhesion molecule 1 (ICAM-1), and reorganization of their cellular F-actin (263). Genetic and biochemical experiments have demonstrated that kaposin A activates the ERK1/2 pathway by recruiting the guanine nucleotide exchange factor cytohesin-1 to membranes, leading to enhanced GTP binding of the GTPase, ARF1 (263).

The K12 locus expresses the most abundant latent transcript(s) in KS tissue and PEL cells and is also strongly induced following lytic reactivation of KSHV (437, 483, 487, 540). The major transcript in this locus initiates at least 2 kb upstream of the K12 ORF, at either of two start sites separated by a 5-kb intron (291, 437). The KSHV genomic sequence between the start sites and the K12 ORF is highly polymorphic in comparisons of viruses from different KS specimens and PEL cell lines, containing a variable number of direct, GC-rich repeats (291, 437). Transcription through these polymorphisms yields RNAs that differ in length by up to 0.8 kb in different isolates; although the only predicted translational start codon within the locus is the AUG of ORF K12, the direct repeats contain CUGs, which are preferentially used for translational initiation (437). Downstream of these CUGs, the direct repeats lack stop codons in all three reading frames, but only one reading frame is open to the end of K12 (437). Hence, the major protein product of this locus is approximately 48 kDa (437); the 6-kDa protein predicted by K12 is detectable only after treatment of BCBL-1 cell lysates with strong reducing agents (263).

K11.5/vIRF2. K11.5 expresses a latent homolog of cellular IRFs (Fig. 1) that inhibits (i) NF-κB and cellular IRF1- and IRF3-mediated transactivation (65), (ii) apoptosis of T-cell receptor (TCR)/CD3-stimulated Jurkat cells (258), and (iii) double-stranded RNA protein kinase (63).

K10.5/LANA-2. K10.5 expresses LANA-2, which inhibits p53-mediated transactivation and apoptosis but is expressed latently only in B cells, not KS tissue (431).

K15/LAMP. One of the two K15 transcripts (Fig. 1) is expressed latently in PEL cells, is a positional homolog of transforming genes in EBV and HVS, and interacts with growth control proteins (discussed above) (101, 184, 407, 460).

Lytic Genes and KSHV Pathogenesis

The vast majority of infected cells in KS lesions express latent viral proteins, whose growth-regulatory properties suggest that they contribute prominently to viral pathogenesis, especially in an autocrine fashion. However, the control of lytic reactivation of KSHV is also a crucial event in the pathogenesis of KS. B-cell infection predicts future development of KS (13), and latent infection by KSHV is established well before the onset of KS (325, 356). In keeping with the KSHV classification, the primary target of viral infection is the $CD19^+$ B lymphocyte (13, 340, 354, 530) (although some other mononuclear cells may also be susceptible to infection [46]). Therefore, reactivation of productive (lytic) KSHV infection from the latently infected B-cell reservoir appears to be a necessary antecedent step in KS development. The presence of KSHV-infected B cells in the peripheral blood (13, 138, 340) and the ability of TPA-treated PEL cells to efficiently transmit KSHV to primary endothelial cells in culture (441) suggest that circulating B cells may help disseminate the virus to extralymphoid targets such as lymphatic endothelium, where the virus then establishes a secondary latent infection (483). Supporting this notion, active KSHV replication and increased viral load in the peripheral blood predicts the pathogenic outcome of the infection (410) and is strongly correlated with (i) increased risk of progression to KS (13, 530) and (ii) increased severity of the pathogenic stage of KS (47, 68). Furthermore, treatment of high-risk patients with the antiviral ganciclovir blocks lytic KSHV replication and reduces KS risk (324). Likewise, AIDS-associated KS regression due to HAART is associated with decreased KSHV loads in the peripheral blood (469, 534) whereas HAART nonresponders fail to clear KSHV from PBMCs (469). Posttransplantation KS is also usually associated with reactivation of KSHV from a latent infection rather than with a primary infection (17, 165, 235, 390). Growth of PEL cells under hypoxic conditions also induces lytic KSHV gene expression, providing a provocative connection between diseases affecting tissue oxygenation (e.g., malaria) and KS progression (121). Conversely, transformation of B cells by KSHV would probably be less dependent on lytic reactivation for dissemination.

Molecular virologic studies support the hypothesis that KSHV reactivation not only enhances dissemination but also potentially contributes directly to KS through expression of

viral lytic genes (81, 155), many of which encode growth-deregulatory and immunomodulatory proteins (specifically discussed below) (156, 233, 236, 393, 444, 489). Numerous lytic proteins also have the potential to enable infected cells to avoid or inhibit the host immune system. Collectively, these viral proteins counteract multiple levels of the immunological response to viral infection and may play dual roles in growth modulation and immune evasion; for example, antiapoptotic proteins could enable infected-cell proliferation while inhibiting destruction by host immunocytolytic activities.

K2/vIL-6. vIL-6 (Fig. 1) retains sequence and functional homology to cellular IL-6 but stimulates multiple cellular pathways to induce cell proliferation and extrahepatic acute-phase responses through engagement of the gp130 coreceptor independently of the IL-6 (gp80) receptor (103, 220, 264, 345, 360, 374, 385, 520). vIL-6, but not human IL-6, protects PELs and heterologous cells from the antiviral, cytostatic effects of IFN-α, which down-regulates the surface expression of gp80 but not gp130 (95). In fact, vIL-6 transcription is induced indirectly by IFN-α in an IE-like fashion through two IFN-stimulated response elements in its promoter (95). vIL-6 induces human IL-6 secretion, supports the growth of IL-6 dependent cell lines, and is an autocrine growth factor for PEL cells (164, 169, 357). Cells stably expressing vIL-6 secrete increased VEGF and induce hematopoiesis, tumorigenesis, and angiogenesis when injected into nude mice (20, 306). In KS specimens, vIL-6 is expressed in a lytic pattern in a minor fraction of infected cells (59, 69, 482, 489).

ORF74/vGPCR. vGPCR (Fig. 1) is a 7-transmembrane, IL-8 receptor homolog that constitutively engages pathways downstream of multiple G protein subunits in a phospholipase C- and phosphatidylinositol 3-kinase-dependent manner. These pathways include protein kinase C, protein kinase B, Akt, NF-κB, and mitogen-activated protein kinases, leading to increased transcriptional activity of their nuclear targets, stimulation of cellular proliferation, promotion of cell survival, and transformation (23, 29, 118, 349, 361, 391, 453, 473). Microarray experiments have shown that the global gene expression response to vGPCR expression is very divergent in B lymphocytes and endothelial cell lines: two CC chemokines were most highly induced in B cells, while IL-6 and GROα were highly induced in endothelial cells (405). In transient transfections, vGPCR also activates the promoters of multiple latent and lytic KSHV genes (100). Ultimately, cells expressing vGPCR secrete increased levels of autocrine and paracrine cytokines and growth factors (IL-1β, TNF-α, IL-6, IL-8, granulocyte-macrophage colony-stimulating factor, VEGF, bFGF, and MCP-1), and produce conditioned medium that is chemotactic (29, 391, 453, 461, 475). In transgenic mice, vGPCR induces multifocal, angioproliferative, KS-like lesions (536), whose high incidence requires agonist modulation of vGPCR by heterologous chemokines (221, 361, 435, 473).

vGPCR is encoded by a major bicistronic transcript that also encodes the K14/viral OX2 (Fig. 1) and by a minor monocistronic transcript and is expressed in PEL cells and infected KS tissue in a lytic pattern (100, 260, 365, 494). Its transcription is controlled by the same promoter as the major latent transcripts, but it is transcribed in the opposite direction (134, 238).

K6/vMIP, K4/vMIP-II, and K4.1/vMIP-III. The vMIP-I, v-MIP-II, and v-MIP-III proteins are homologs of human MIP-Iα, a βCC chemokine. While vMIP-I is most probably a product of DE transcription (353, 374), vMIP-II and vMIP-III are encoded together on an IE mRNA (542)(Fig. 1).

Numerous proinflammatory roles have been attributed to the viral chemokines. vMIP-I and vMIP-II both engage the chemokine receptor CCR-8 (120, 214, 480) and are highly angiogenic in chicken CAMs (50). Treatment of PELs with vMIP-I induces the secretion of VEGF-A, and dexamethasone-induced apoptosis of PELs is blocked by exogeous vMIP-I and vMIP-II (306). vMIP-III engages the CCR-4 chemokine receptor, is a selective chemoattractant for Th2 cells, and is also angiogenic in CAM assays (485). Paradoxical to the synergistic pathogenesis of KSHV and HIV-1, vMIP-I and vMIP-II can inhibit CCR3- and CCR5-dependent HIV-1 infection (50, 262, 353).

vMIP-II has been implicated in the seemingly contradictory function of both immune evasion and proinflammation; its biological function therefore remains controversial. It is a broad antagonist (binding without activation) of endogenous chemokine signaling (120, 315) and chemotaxis (262), but others have shown that it selectively activates and chemoattracts eosinophils, Th2 cells, monocytes, and endothelial cells (50, 214, 480). However, when human DMVEC monolayers were used under "flow" conditions, vMIP-II blocked chemotaxis of monocytes and Th1 lymphocytes by antagonism of CCR1 and CCR5 and blocked chemotaxis of eosinophils and Th2 lymphocytes by antagonism of CCR3 (527).

K9/vIRF-1 and K10.5/K10.6/vIRF-3. In addition to the latently expressed vIRFs discussed above, KSHV encodes two other homologs of these proteins (Fig. 1). vIRF-1, encoded by K9, transforms cells in culture, is tumorigenic in nude mice, and inhibits apoptosis induced by Sendai virus infection, IFN-α, IFN-β, TNF-α, TCR/CD3 cross-linking, and p53 (64, 160, 174, 234, 258, 293, 302, 369, 456, 457). It also blocks programmed cell death mediated by cooperation of the cellular protein GRIM19 with IFN-β and retinoic acid (456).

Although vIRF-1 does not directly bind to DNA, it activates transcription when targeted to promoters by a heterologous DNA binding domain (432); in fact, direct transactivation of the c-*myc* promoter by vIRF-1 is required for transformation, and CBP coactivates c-*myc* with vIRF-1 (234). However, vIRF-1 has been best characterized for inhibiting the transcriptional programs induced by exogenous IFNs (174, 293), specifically by blocking transcriptional activation by the cellular proteins IRF-1 and IRF-3. This is mediated by multiple mechanisms, including direct binding of vIRF to its cellular homologs, competitive binding to the transcriptional coactivator p300, and inhibition of the histone acetyltransferase activity of p300 (64, 160, 258, 292, 302, 550). vIRF-1 also directly binds p53 to inhibit its phosphorylation and acetylation and blocks its ability to transactivate transcription (369, 457). Antisense inhibition of K9 expression in PELs demonstrated a critical role for IRF-1 in reactivation of KSHV from latency and lytic gene expression (293). The other lytic viral IRF, vIRF-3, is most closely related to the cellular IRF-4 and the latent vIRF-2 and also blocks IFN signaling by functioning as a dominant negative inhibitor of IRF-3 and IRF-7 (309).

K1. K1 encodes a transforming and immunomodulatory protein; it is the most highly divergent ORF in the KSHV genome and is discussed in full above.

ORF16/vBCl-2. The product of KSHV ORF16 retains highest sequence similarity to human bcl-2 in its BH1 and BH2 domains but little similarity in the BH3 domain (98, 446). It is expressed in a lytic pattern in spindle cells and monocytes in KS lesions, and its transcript is lytically induced in PEL cells (Fig. 1), although the protein has evaded easy detection there (98, 446, 533). As predicted by sequence homology, vBcl-2 is antiapoptotic; unlike its cellular counterpart, it can inhibit apoptosis induced by KSHV vCyc in the presence of high cdk6 (378). Also unique to vBcl-2, it cannot be converted to a proapoptotic form by caspase-mediated cleavage (36). In rabbit reticulocyte lysates, vBcl-2 does not directly interact with cellular Bcl-2 family members, but in yeast two-hybrid assays, it does interact with cellular Bcl-2; it also partially reverses cell death induced by Bax (98, 446). The antiapoptotic mechanism of vBcl-2 may be attributable to its interaction with the proapoptotic cellular protein Diva, which binds to the caspase-9 regulator Apaf-1 to prevent Bcl-XL from blocking cell death (228).

K7/vIAP. The product of K7 (Fig. 1) is a homolog of the cellular protein survivin-ΔEx3 and is not conserved in other close relatives of KSHV (522). Both proteins contain a BH2 domain and a partial baculovirus inhibitor of apoptosis protein (IAPs) repeat domain. The 19- to 21-kDa glycoprotein product of K7 localizes to mitochondrial membranes and inhibits apoptosis induced by the Fas and TRAIL pathways, Bax, TNF-α plus CHX, staurosporine, ceramide, and other chemicals (158, 522). Mechanistically, vIAP targets two critical arms of the early and late cellular apoptotic response. It acts as a protein bridge to help target Bcl-2 to activated caspase-3 to inhibit its function as an effector of cell death (522). It also binds to the cellular calcium-modulating cyclophilin ligand to enhance the cytosolic Ca^{2+} flow and protect cells from mitochondrial damage and apoptosis (158).

K3/MIR1, K5/MIR2. The modulators of immune recognition (MIRs) are eponymous proteins that actively eliminate the cell surface expression of receptors recognized by the cytolytic arm of the immune system. Both MIR1, encoded by K3, and MIR2, encoded by K5, specifically increase the rapid endocytosis of mature major histocompatibility complex MHC class I from the surface of infected cells and stimulate its degradation by cellular proteases; MIR2 but not MIR1 also stimulates the scavenging of B7.2 and ICAM-1 proteins from the surface (112, 113, 212, 213, 231, 232, 394). The K3 and K5 products are endoplasmic reticulum proteins that both contain plant homeodomain ring finger motifs (similar to those found in cellular E3 ubiquitin ligase proteins), a single transmembrane domain, and a tyrosine-based sorting motif that is a candidate target for cellular adaptor molecules in intracellular sorting (112, 114, 212, 231, 232, 335, 394). Both MIR proteins selectively target MHC class I but not class II; however, although K3 targets all four HLA allotypes, K5 specifically targets HLA-A and HLA-B (232). Target specificity is determined by the transmembrane domain and cytoplasmic tail of the respective target proteins (114, 231, 232), and dominant negative dynamin mutants that inhibit endocytosis block the functions of K3 and K5 (112, 113). Cells expressing K5 are impaired in the induction of CD28-dependent and independent T-cell stimulation (113) and in the stimulation of activity of NK cell lines (231), but not primary NK cells (113).

Despite their homology to each other, MIR1 and MIR2 may function by related but different mechanisms. As predicted by its PHD domain, MIR2/K5 is an E3-ubiquitin ligase that stimulates the ubiquitylation of lysines in the C termini of its cellular targets, in a ring finger-dependent fashion (114). However, the inability to detect ubiquitylated MHC class I complex in response to MIR I/K3 expression has led to the suggestion that the direct target of ubiquitylation by K3 is not the MHC class I molecule and that cysteine and aspartyl proteases, but not the ubiquitin proteasome, mediate MHC class I degradation (308). MIR1/K3 dominantly targets MHC class I complexes to dense lysosomal compartments via the *trans*-Golgi network, in a fashion that requires an intact diacidic cluster and tyrosine-based signaling motif in K3, respectively (335).

K3 and K5 are both expressed in KS tissue in a lytic pattern, and K3 has been detected as part of a bicistronic transcript in a screen for IE gene expression in PEL cells (213, 430). The K5 transcript expression is resistant to low, but not high, concentrations of CHX in PEL cells (212) but has not been detected as an IE product in subtractive screens (430, 542).

K14/viral OX2. K14 (Fig. 1) encodes a homolog of the cellular OX2 protein, a glycosylated cell surface protein that is a member of the immunoglobulin superfamily and restricts cytokine production in a paracrine fashion. Viral OX2 shares all of these structural features but instead potently activates inflammatory cytokine production (IL-1β, TNF-α, and IL-6) from primary, PBMC-derived monocytes/macrophages and dendritic cells (105). It cooperates in paracrine induction with IFN-γ when added solubly to media or when expressed stably on BJAB (B-lymphocyte) cells (105).

LYTIC REACTIVATION OF KSHV

Among a number of KSHV genes tested, only forced overexpression of the product of the ORF50 gene, a protein named Rta, can reactivate the virus from latency in PEL cells (194, 311, 312, 490). The major ORF50 transcript is expressed with IE kinetics (489, 542) and is tricistronic, also encoding the downstream genes K8/K-bZIP/RAP and K8.1 (203, 303, 312, 454, 490, 542). Alternative splicing events in the downstream exons also leads to the expression of two minor tricistronic transcripts (542). The ORF50 locus has thus been deemed the major IE locus because two noncoding RNAs are transcribed antisense to Rta in an IE fashion (311, 448, 542) and the K8 gene is also transcribed with IE kinetics independently of the upstream ORF50 gene (448). As expected, the Rta transcript is expressed in a lytic pattern in KS lesions (248, 489).

ORF50 encodes a 691-aa nuclear polypeptide (Fig. 3) that is highly posttranslationally modified, including extensive phosphorylation (311, 312). Transient transfections demonstrate that Rta directly but selectively transactivates KSHV promoters that are expressed with later kinetics during reactivation (89, 97, 238, 310–312, 477, 524, 525, 537). The C terminus of Rta contains four repeats of alternating acidic and bulky hydrophobic amino acids, a primary structure conserved with many eukaryotic transcriptional activation domains (311), and is sufficient to strongly activate transcription when targeted to promoters with a heterologous DNA binding domain (311, 454, 524) (Fig. 3). Deletion of the activation domain generates a truncated mutant of Rta that forms mixed multimers with

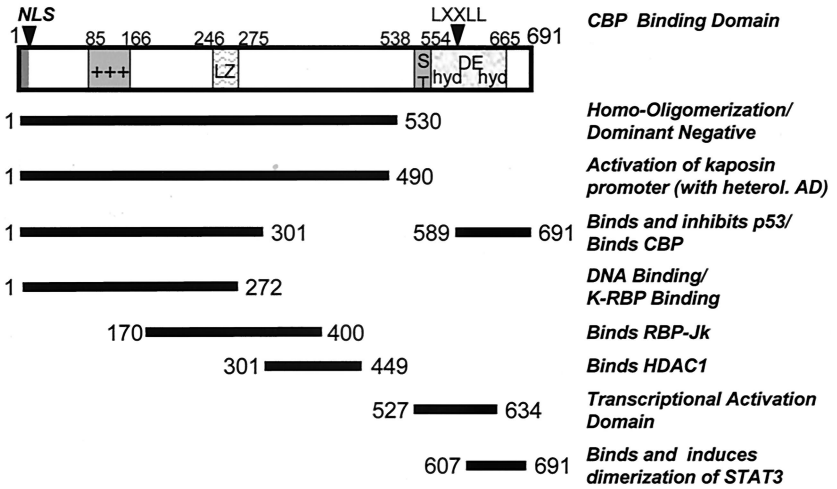

FIG. 3. Primary structure-function map of KSHV ORF50/Rta protein. This schematic shows a linear representation of the amino acid content and predicted structural motifs of the ORF50/Rta protein. The amino acid numbering is as published in reference 436. The approximate position of each functional domain is shown by a black bar, with amino acid boundaries indicated by numbers, corresponding to the function shown in the column on the right (see the text for references). Abbreviations: +++, basic amino acid rich; LZ, putative leucine zipper; ST, serine/threonine-rich; hyd/DE/hyd, repeats of hydrophobic and acidic amino acids, as in reference 311 and described in the text.

wild-type Rta and functions as an ORF50-specific dominant negative inhibitor of transactivation (311). Furthermore, expression of the truncated Rta in transfected BCBL-1 (PEL) cells, in the context of physiologic levels of endogenous ORF50 expressed from the viral template, potently suppresses spontaneous reactivation from latency and strikingly suppresses viral replication induced by TPA, sodium butyrate, and ionomycin (311). The dominant negative Rta truncation mutant thus demonstrated that (i) transcriptional transactivation by ORF50/Rta is not only sufficient but also essential for viral reactivation and (ii) multiple reactivation signals that function using different biochemical mechanisms all converge at ORF50/Rta and require downstream transactivation by Rta to successfully reactivate the virus (311). Similarly, methotrexate treatment of PEL cells inhibits the expression of Rta, the activation of genes downstream of Rta, and viral reactivation (119).

ORF50/Rta binds to several viral promoters in a sequence-specific fashion (89, 126, 295, 310, 476, 477; S. Lynch, K. Driscoll, D. Palmeri, and D. M. Lukac, unpublished observation), yet direct DNA binding by Rta is not sufficient to specify a promoter as a target of ORF50/Rta-mediated transactivation; instead, specificity appears to be governed by combinatorial interactions with cellular proteins. Rta binds directly to a palindromic sequence shared by the ORF57/Mta and K8/K-bZIP/RAP promoters, and the N-terminal 272 aa of Rta is sufficient for binding in vitro (310) (Fig. 3). However, genetic and biochemical experiments demonstrate that transactivation of the Mta promoter by Rta requires a direct interaction with the sequence-specific DNA binding protein RBP/Jk (also known as CBF-1 and CSL); transactivation of this promoter is enhanced by DNA binding of Rta to its element (295, 310). RBP-Jk-binding sites also mediate Rta-driven activation of the promoters of KSHV ORF6/single-stranded DNA binding protein and thymidine kinase (295; Lynch et al., unpublished). Similarly, in vitro experiments demonstrate that the DNA binding domain of Rta (aa 1 to 272) (310) is sufficient to bind to a heterologous element shared by the viral PAN and K12/kaposin A promoters (477, 478), yet fusion of this polypeptide to a heterologous activation domain is not sufficient to transactivate the kaposin promoter in vivo (89). Instead, activation requires aa 1 to 490 of Rta in this context (89), a region of Rta that probably interacts with other cellular DNA binding factors (Fig. 3). Furthermore, autoactivation of the proximal ORF50/Rta promoter by Rta (127, 194, 454) requires an interaction with the cellular protein octamer-1 (but not octamer-2) and an intact octamer element that is located approximately 200 bp upstream of the ORF50 transcription start site (440).

Numerous other protein-protein interactions modulate transactivation mediated by ORF50/Rta. KSHV Rta binding protein (K-RBP) is a ubiquitously expressed cellular protein that contains homology to Krueppel-associated box-zinc finger proteins and synergizes with Rta in transactivation of the promoters of KSHV Mta, K8/K-bZIP/RAP, K6/vMIPI, and Rta itself (525). K-RBP interacts directly with a DNA binding fragment of Rta, but their combinatorial transactivation mechanism has not yet been described. The cellular Jun protein cooperates with ORF50/Rta through a mutual interaction with the coactivator CBP (208). A DE target of ORF50/Rta, the posttranscriptional activator protein ORF57/Mta (Fig. 1), uses an uncharacterized mechanism to synergize with Rta in a promoter-specific fashion (259). Repression of Rta-mediated activation has also been demonstrated for the E1A protein by competition for CBP and for HDAC1, which binds to a central region of Rta (208).

Since Rta is essential for viral reactivation (311), it follows that all, or a subset, of its direct targets of transactivation will also be essential for lytic reactivation of KSHV. The observation that Rta directly transactivates the promoters of many of the candidate pathogenic genes of KSHV, including K12/kaposin, vIL-6, vMIP-I, vIRF-1, vGPCR, and K1 (55, 97, 119, 126, 507, 525), suggests that the ability of these proteins to abrogate normal cellular growth control and physiology is es-

sential for optimizing the cellular and anatomical milieu for viral replication. Likewise, activation of cellular IL-6 (125) by Rta and the ability of Rta to block p53-mediated apoptosis by competing for binding to CBP (209) confirm that Rta also targets cellular pathways of growth control. Concordant with the orchestration of the KSHV lytic cycle by Rta and pathogenic progression, Chen et al. demonstrated that the promoter controlling the expression of ORF50/Rta is repressed by methylation and is demethylated by inducing signals; clinically, the ORF50/Rta promoter in a latent KSHV carrier was highly methylated, while it was virtually unmethylated in most patients with MCD, PEL, and KS (96).

Thus, lytically infected cells may serve not only as reservoirs of infectious virus but also as reservoirs of viral proteins that influence cell proliferation in a paracrine fashion. This presents a paradox, since (as discussed above) host cells that are stimulated to reactivate KSHV succumb to virus-mediated lysis during productive replication. However, a slow or inefficient lytic cycle, allowing a prolonged period of viral delayed-early gene expression prior to viral cell lysis, would be consistent with such a model. Indeed, reactivation of KSHV in one cultured endothelial cell model displays just such a slow lytic phase (106). Nonproductive, abortive reactivation might also be expected to enhance cell growth.

Putative reservoirs of KSHV lytic gene expression may thus function to recruit and stimulate the proliferation of immune cells (by paracrine factors like the vMIPs, vIL-6, and viral OX2) at sites of viral replication, potentially to increase the availability of target cells permissive for viral replication. Recruitment and stimulation of target cells to enhance their permissiveness has been documented for other herpesviruses such as human and murine cytomegalovirus (261, 438) and equine herpesvirus type 1 (509). Supporting this hypothesis, the addition of inflammatory cytokines to cultured human peripheral blood leukocytes from KSHV-positive patients is essential for maintenance of persistent viral infection in these cells (155, 347, 468). The spontaneous reactivation of the virus in a characteristic small percentage of cells, evident in every KS specimen, as well as infection of PELs and endothelial cells, is also consistent with the requirement for low-level lytic-gene expression in maintenance of the infected-cell population. Translated to the clinical setting, this may represent a pathogenic mechanism by which KSHV initiates or maintains the aggressive inflammatory infiltrate that characterizes KS lesions.

Furthermore, many of the cytokines known to reactivate KSHV in PEL cells, including oncostatin M, hepatocyte growth factor, IFN-γ, IL-6, HIV-1 Tat, and an unidentified soluble factor released from HIV-1-infected cells (43, 88, 224, 339, 347, 476, 510), are expressed in KS lesions (reviewed in reference 154) and are also required as growth factors for spindle cells (66, 153, 341, 368), suggesting that reactivation of KSHV from latency may be coregulated with stimulation of target cells.

PERSPECTIVES AND FUTURE DIRECTIONS

Although ORF50/Rta can autoactivate its own expression (127, 194, 440, 454), little is known about the direct effect of the other physiologic reactivation signals on either the induction of ORF50 expression or its subsequent function during reactivation. Functional interactions of ORF50/Rta with numerous heterologous proteins have been demonstrated in uninfected cells, but their relevance to viral reactivation and replication remain unevaluated. The expression or regulation of the binding partners of ORF50/Rta will probably provide a significant regulatory step in the success or efficiency of reactivation of the virus to productive replication. Such regulation could impact the potential for Rta expression in the absence of productive replication, the induction of "sublytic" gene expression programs during reactivation, the period of DE growth-deregulatory gene expression prior to lysis, or the uniformity of latently infected cell populations to permissively support reactivation.

Does ORF50/Rta integrate all of the viral "reactivation" signals that induce lytic gene expression and/or viral replication? Chatterjee et al. recently demonstrated that IFN-α directly induces vIL-6 from latent KSHV in an IE fashion (95); the lack of any other detectable viral gene expression suggests that lytic genes can be induced in the absence of ORF50/Rta. Therefore, some signaling pathways can bypass ORF50 to activate DE genes, providing a mechanism by which viral growth-stimulating genes can be induced independently of productive reactivation, and cell lysis. The response of Rta expression or function to a particular signal might thus determine the fate of an individual infected cell to serve exclusively as either a reservoir of progeny virus or lytic growth factors.

A second provocative aspect of KSHV biology is the conservation of multiple viral genes with the potential for counteracting the IFN response of the host. Even more provocative is that the virus has also conserved positive modulators of the host IFN response, suggesting that a subset of IFN-inducible cellular activities are essential for viral replication and may promote permissive infection. Thus, the broad induction of many IFN-responsive genes following de novo infection of endothelial cells by KSHV (359, 406) probably is not attributable solely to the classic mammalian antiviral response. Indeed, two viral proteins, one latent and one lytic, actively stimulate interferon target genes. Microarray analyses of the global effects of LANA-1 expression in B cells demonstrated that 5 of 15 transcripts up-regulated at least twofold were from IFN-stimulated genes, in the absence of detectable effects on the IFN-α or IFN-β itself (421). Likewise, the lytic switch protein ORF50/Rta functions as a ligand-independent activator of STAT3 by directly binding to it, recruiting it to the nucleus, stimulating its dimerization, and activating the transcription of STAT-driven reporter genes (210). In fact, IFN-γ alone has proviral effects on KSHV replication, demonstrated by the induction of lytic reactivation of latent KSHV by the addition of IFN-γ to the growth media of cultured PEL cells (43, 88, 339) and the promotion of maintenance of persistent KSHV infection by IFN-γ addition to primary explanted PBLs (155, 347, 468). In agreement, early attempts to treat KS patients with IFN-γ were associated with progression of disease (172, 271), suggesting that this cytokine promoted viral replication in infected people.

Conversely, IFN-α has antiviral effects on KSHV infections in PEL and explanted PBL models (88, 346), as well as in clinical settings (274), affirming that only specific IFN-induced products can be usurped by the virus to its advantage. For example, IRF7, a critical protein in the cellular response to

IFN-α, is one of the most strongly induced transcripts following de novo KSHV infection (406), but the virus expresses ORF45, an IE gene product that blocks IRF-7 phosphorylation and nuclear accumulation (543). vIL-6 also plays a novel role in the ability of KSHV to escape the antiviral effects of IFN-α (95).

Remarkably, the virus has conserved four lytic and latent antagonistic homologs of IRFs. This seeming redundancy in anti-IFN functions may reflect the requirement for the virus to temper the IFN response so that it does not exceed the threshold at which it is beneficial for replication. Alternatively, the individual viral modulators of the IFN pathway may have been conserved to target very specific regulators of the response, stimulating the functions beneficial for the virus while blocking the harmful ones. Supporting this hypothesis, K9/vIRF-1 is both an antagonist of cellular IRFs and well as a transcriptional activator and is essential for efficient lytic gene expression during reactivation (293). A key question that remains, however, concerns the mechanism(s) by which specific IFN-induced cellular genes have a proviral effect. One clue may come from models of mouse cytomegalovirus infection, in which a G_1 cell cycle arrest following IFN induction is essential for viral DNA replication (219, 434).

Many of the questions concerning the requirement for latent and lytic gene expression in KSHV pathogenesis will be addressable with newly described systems for de novo infection of endothelial cells (106, 130, 278, 358). Combining such systems with tenable genetic approaches for generating viral mutations, such as bacmid clones of full-length KSHV (61, 123, 541), will allow precise determination of gene functions during infection by using knockouts and deletions of viral genes and critical *cis* elements, as well as knockins to replace wild-type viral genes with mutants and variants. The contribution of the latent and lytic cycles to pathogenesis in endothelial cells, the effects of expression of the pathogenic latent and DE genes in the context of viral infection, and the determination of genetic requirements and gene expression kinetics during de novo infection and establishment of persistence, can all be realized.

The PEL models remain the most robust systems for understanding KSHV persistence and reactivation from latency. Since most PEL cells are dually infected with latent KSHV and EBV (reviewed in reference 138), this suggests that B-cell reservoirs of KSHV may also be EBV infected in vivo. Furthermore, KSHV LANA-1 can modulate the expression program of the EBV latent genes: it potently activates the promoter of the EBV LMP-1 gene (202) (a constitutive signaling and transformation protein [reviewed in reference 256]) but reduces the expression of EBV EBNA-1 (the LANA-1 ortholog) and represses EBV EBNA-2 activation of a second latency promoter (273). Likewise, the KSHV lytic switch protein Rta binds to RBP-Jk (295), a key cellular target of the EBV latent transforming program (256), and in dually infected PEL cells, KSHV and EBV can be selectively induced from latency (342, 490). As additional functional mechanisms of the KSHV proteins are revealed, interesting insights into cross-regulation of the two viruses could contribute to a greater understanding of the unique KSHV-associated diseases.

Little is known about primary infection by KSHV and the progression of KS in the absence of coinfection with HIV. Future prospective studies of African children, including disease progression (Kaplan-Meier analyses) and subtype-specific infection, should be revealing. In the West, the risk factors for infection in the 3 to 10% of the general population who are seropositive are currently not understood, nor are the geographic risk factors that stratify the Mediterranean populations. These insights are crucial for reducing the risk of KSHV transmission, infection, and disease in humans, while the molecular studies and animal models will continue to reveal the unique mechanisms of this pathogen and targets for treatment.

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