

KAPOSI'S SARCOMA—ASSOCIATED HERPESVIRUS: A New DNA Tumor Virus

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■ **Abstract** Kaposi's sarcoma-associated herpesvirus (KSHV) is a newly identified gammaherpesvirus associated with all clinical forms of Kaposi's sarcoma (KS), body-cavity-based, primary effusion lymphomas (PELs), and a subset of Castleman's disease (CD). Sequence analysis of the KSHV genome demonstrates an extensive array of genes with homology to cellular genes involved in cell cycle regulation, cell proliferation, apoptosis, and immune modulation. Functional studies indicate that these genes may modify the host cell environment, contributing to the pathogenesis of KSHV-associated disorders. Several KSHV genes have been found to cause dysregulated cell proliferation or to interfere with established tumor suppressor pathways. The epidemiologic association of KSHV with malignancies and the coding features of its genome suggest that it is a new DNA tumor virus.

INTRODUCTION

Kaposi's sarcoma (KS) remained a rare curiosity to clinicians and cancer researchers for over 100 years before it shot to prominence as the sentinel diagnosis of AIDS. In 1872, the Austrian-Hungarian dermatologist Moritz Kaposi published the case histories of five patients with "idiopathic multiple pigmented sarcomas" of the skin (1). This form of the disease was designated Kaposi's sarcoma in 1891 at the suggestion of another prominent dermatologist of the time, Kobner, and is now called classic KS. Classic KS occurs predominantly in elderly male patients of Southern European ancestry. A high frequency is also seen in Israel and other Middle Eastern countries.

KS existed for many decades before HIV in some equatorial countries of Africa. This form, referred to as endemic KS, is found in younger patients as well as the elderly, and is generally a more aggressive disease than classic KS (2). In particular,

endemic KS in African children is associated with prominent lymphadenopathic involvement. The majority of these children die from the disease (3).

During the past 20 years, the incidence of KS among renal transplant recipients and other patients receiving immunosuppressive therapy (known as post-transplant KS or iatrogenic KS) has increased. Patients of Mediterranean, Jewish, or Arab ancestry are over-represented among immunosuppressed patients who develop KS in this setting (4).

In 1981, the US Centers for Disease Control and Prevention (CDC) became aware of an increased occurrence of two rare diseases in young gay men from New York and California: KS and *Pneumocystis carinii* pneumonia (5). This ushered in the AIDS epidemic, and today AIDS-KS is the most common form of KS. In many HIV-seropositive individuals, immunosuppression leads to the clinical presentation (or manifestation) of KS, which starts with a few skin lesions but without treatment often develops into disseminated disease affecting various organs including lung, liver, gut, and spleen.

THE KAPOSI'S SARCOMA "AGENT"

Studies of AIDS case surveillance data support the existence of a sexually transmissible KS cofactor. Among AIDS patients, KS occurs predominantly in gay and bisexual men, less commonly in those who acquired HIV through heterosexual contact, and rarely in hemophiliacs or intravenous drug users (6). However, a viral etiology for this tumor was suspected long before the onset of the AIDS epidemic (7). In 1972, electron microscopy revealed herpesvirus-like particles in KS tumor cells, which were later attributed to cytomegalovirus (CMV) (8, 9). Subsequently, DNA sequences of CMV, human herpesvirus-6 (HHV-6), human papilloma viruses, and BK virus (also called human polyoma virus), as well as other viral (including retroviral) or bacterial pathogens, have all been detected in KS lesions and suspected to be agents of KS (10–12). However, these agents, including CMV, HHV-6, and papilloma viruses, are only found in some lesions, and BK virus is a ubiquitous agent present in many tumors and tumor cell lines (13).

A NEW HERPESVIRUS: Kaposi's Sarcoma-Associated Herpesvirus (KSHV)

Chang et al employed representational difference analysis, a PCR-based subtractive hybridization method, to identify sequences of KSHV (14). Initial analysis allowed KSHV to be classified as a gammaherpesvirus (genus *Rhadinovirus*) (15) with sequence similarity to several other oncogenic gammaherpesviruses, including herpesvirus saimiri (HVS) and Epstein-Barr virus (EBV). These herpesviruses are transforming agents that cause tumors in their hosts or in experimental animals.

The genome of KSHV was subsequently mapped and sequenced by Russo et al using cosmid and lambda phage genomic libraries from a PEL-derived cell line, BC-1, stably coinfecting with KSHV and EBV (16). The KSHV genome consists of an estimated 140.5-kb long unique coding region flanked by terminal repeat sequences. More than 85 open reading frames (ORFs) have been identified, including 66 with sequence similarity to HVS ORFs. Nonconserved genomic regions contain a wide array of homologs to cellular genes (16). Neipel et al generated a second sequence of a KSHV genome, derived from a KS lesion, which is virtually identical to the KSHV strain in the BC-1 lymphoma cell line (17). Examination of select regions of the KSHV genome from numerous KS lesions and PEL cell lines led Hayward et al to propose four variant genotypes, A, B, C, and D, based on the K01 gene (18), and two allelic forms, primary (P) and minor (M), based on the K15 gene (19). The geographic distribution of these virus genotypes has been interpreted to support the notion that KSHV is an ancient human herpesvirus that has diversified under selection pressures following the migratory divergence of host human populations.

Subsequent to the discovery of KSHV, several new nonhuman primate rhadinoviruses were isolated that appear to have an even closer phylogenetic relationship to KSHV than either HVS or EBV. These new members define two distinct rhadinovirus lineages. One lineage is closely related to KSHV and includes retroperitoneal fibromatosis herpesvirus (20), *Chlorocebus* rhadinovirus 1 (ChRV1) (21), and some chimpanzee and gorilla rhadinoviruses (PanRHV1, PanRHV2, GorRHV1) (22). The second lineage includes a rhesus monkey rhadinovirus (23) and ChRV2 (21). The finding of two lineages of rhadinoviruses in nonhuman primates raises the issue of whether there is also an unidentified RRV/ChRV2 type virus in humans.

MOLECULAR DETECTION

An overwhelming number of polymerase chain reaction (PCR) studies have determined that KSHV is found in all clinical subtypes of KS lesions but is generally absent in non-KS tissues from KS patients, in other vascular neoplasms, and in other forms of skin tumors from immunosuppressed patients (for review see 24). Exceptions include saliva and blood (25). In peripheral blood mononuclear cells, KSHV DNA can be detected by PCR in approximately 50% of KS patients. Further, KSHV detection in peripheral blood mononuclear cells of HIV-seropositive individuals can predict who will subsequently develop KS (26, 27). Although one group reported the frequent detection of KSHV in the semen of healthy Italian donors (28), KSHV is not detectable in semen donors in North America and the United Kingdom and only rarely in patients with KS (29–32). Reports of KSHV detection in bone marrow stromal cells of multiple myeloma patients and in sarcoid tissues are controversial and have not been confirmed (33–37).

SEROEPIDEMIOLOGY

Immunofluorescence, western blot, and ELISA assays to detect antibodies against KSHV latent and lytic antigens have been developed. Most current testing uses assays that detect antibodies against the major latency-associated nuclear antigen (LANA) in conjunction with one of the lytic antigens encoded by ORF65 or K8.1 (38–40). These serologic tests demonstrate that individuals with KS (or at risk of developing KS) are more likely to have detectable antibodies to KSHV in their sera and that infection precedes development of clinical KS (41–43). Although some early assays estimated the prevalence of KSHV infection in general blood donors to be as high as 25% (44), the accumulating evidence suggests that the seroprevalence of the general population in the North American, European, and Asian countries is actually <5% (40, 43, 45–47). Agreement exists that infection by KSHV, unlike most other herpesviruses, is not ubiquitous.

Although the exact risk factors for acquisition of KSHV infection remain elusive, epidemiologic serosurveys indicate that KSHV is largely transmitted sexually in the United States and Northern European countries. In the San Francisco Men's Health Study, Martin et al found that the prevalence of KSHV infection is high among homosexual men and correlates with the number of homosexual partners (48). In the Amsterdam Cohort Study (1984–1996), Dukers et al found strong evidence for orogenital transmission of KSHV among homosexual men (49). From this same cohort, HIV-infected individuals who seroconvert to KSHV after acquiring HIV have a higher risk for developing KS (hazard ratio 5.04–95% CI: 2.94–8.64) than HIV-infected individuals with KSHV antibodies prior to or concurrent with their acquisition of HIV (hazard ratio 3.15–95% CI: 1.89–5.25) (50). In African countries however, the transmission of KSHV appears also to occur by casual routes, with antibodies against KSHV detectable in children (probably acquired by horizontal transmission) (51–53) and increasing with age (54–56).

KAPOSI'S SARCOMA: Histogenesis and Clonality

Histologically, KS is a complex lesion composed of interweaving bands of spindle cells that form irregular vascular channels. These lesions are frequently associated with an inflammatory infiltrate. Because spindle cells form the bulk of established KS lesions, they are thought to represent the neoplastic component, but controversy exists over the histogenesis of these cells. Although the majority of the spindle cells stain positive for endothelial cell markers, including Factor VIII and CD34, other cells express proteins characteristic of smooth muscle cells, macrophages, or dendritic cells (57, 58). Some spindle cells simultaneously express antigenic determinants of several different cell lineages, suggesting that KS spindle cells might be derived from a pluripotent mesenchymal progenitor cell or a mesenchymal cell with anomalous differentiation. Several antibodies against viral proteins have been found to be suitable for tissue localization studies. The major viral

LANA encoded by ORF73 appears to be expressed in virtually all KSHV-infected cells (59–61).

The evolving nature of KS lesions, in concert with instances of occasional spontaneous remission, has led to the notion that KS may represent a reactive hyperplasia rather than a true malignancy. Studies analyzing X chromosome inactivation patterns have produced varied results that suggest monoclonal patterns of inactivation in some KS lesions and polyclonal patterns of inactivation in others (62–64). Although this technique is PCR-based and therefore quite sensitive, it suffers from the infiltrative growth pattern of KS lesions that frequently leads to the incorporation of normal tissues or cells in the analysis. Recently, a terminal repeat analysis assay using pulsed field gel electrophoresis has been used to determine viral clonality in KSHV-infected disorders. Although this study did not report findings from early or multicentric KS lesions, 6/16 (38%) nodular KS lesions showed monoclonal, oligoclonal, and polyclonal patterns of viral infection (65).

The histologic, clinical, and molecular features would be reconciled by a model for KS in which early lesions are nonclonal, possibly virus-infected proliferations of endothelial cells or endothelial precursors, and advanced disease represents oligoclonal or monoclonal neoplasms. This model is comparable to EBV-driven polyclonal lymphoproliferative disorders in immunodeficient individuals, which can progress to clonal lymphomas. The contribution to pathogenesis of lytically replicating virus in a subset of KS spindle cells has not been determined; however, a paracrine model for neoplasia, in which viral gene products expressed in one cell may affect the growth characteristics of surrounding cells, has been suggested (65a).

KSHV AND LYMPHOPROLIFERATIVE DISORDERS

Body Cavity–Based Primary Effusion Lymphomas

Knowles et al first recognized the unique aspects of some effusion-based lymphomas in patients with AIDS (66). Subsequently Walt et al described similar cases (67). The cells in these cases were negative for most lineage-associated antigens, although gene rearrangement studies indicated a B cell origin with clonal rearrangement of the immunoglobulin genes. Karcher et al further demonstrated the distinctiveness of the syndrome, reporting a high prevalence of EBV and absence of *c-myc* rearrangements (68). They also noted the tendency of the disease to remain confined to body cavities without further dissemination. Concurrent with the identification of KSHV in KS, KSHV was first detected by Chang et al in three of these distinctive lymphomas (14). This finding was later followed up by a comprehensive report (69), which found that KSHV was associated specifically with body cavity–based primary effusion lymphomas (PELs) but not with other Hodgkin's and non-Hodgkin's lymphomas.

PELs possess a unique constellation of features that distinguishes them from all other known lymphoproliferations. PELs present predominantly as malignant

effusions in the visceral cavities, usually without significant tumor mass or lymphadenopathy. These lymphomas occur predominantly in HIV-seropositive individuals with advanced stages of immunosuppression (70) but are occasionally seen in HIV-seronegative patients (71–73). Like KS, with which they are closely linked, PELs are seen primarily in gay men (71, 74). PELs usually do not express surface B cell antigens except for CD138/syndecan-1, a molecule selectively associated with late stages of B cell differentiation (75). This finding and the lack of expression of BCL-6, specific to germinal center B cells, define PEL cells as preterminally differentiated, post-germinal-center-stage B cells (76).

PEL cells consistently lack molecular defects commonly associated with neoplasia of mature B cells, including activation of the proto-oncogenes *c-myc*, *bcl-2*, *bcl-6*, *n-ras*, and *k-ras*, as well as mutations of p53 (71, 77). Southern blot analysis of PEL cells shows the presence of the KSHV genome in very high copy number (50–150/cell) compared with that seen in KS. Cell lines from PELs have been established (78–82). Some cell lines are positive for KSHV only; others are coinfecting with EBV. In addition to cell lines established from lymphomatous effusions, the BCP-1 cell line was established from the peripheral blood of a patient with PEL, which suggests that the malignant cells are present not only in the malignant effusions but also in the peripheral blood (83).

Castleman's Disease

Castleman's disease is a rare and usually polyclonal hematomalymphoid disorder thought to be mediated by interleukin (IL)-6 overexpression (84–86). Two distinct histopathological variants with different clinical characteristics have been described: the hyaline vascular type and the plasma-cell variant. The more common hyaline vascular type usually presents as a solitary mass in the mediastinum or retroperitoneum and is frequently curable by surgical resection. The rarer plasma cell variant often presents with generalized lymphadenopathy, B symptoms, and immunological abnormalities. The systemic variety, also designated multicentric Castleman's disease (MCD), is typically of the plasma-cell variant. An increased risk for developing KS and B cell lymphomas is noted in patients with MCD (87).

Soulier et al were the first to report the presence of KSHV in MCD biopsies (88). They found KSHV in 14 out of 14 lesions from HIV-seropositive French patients with MCD. These included plasma cell, hyaline vascular, and mixed variants. Among HIV-seronegative cases, 7 of 17 lesions were positive for KSHV. Other investigators have since confirmed the presence of KSHV in Castleman's disease biopsies and its association with the MCD variant in HIV-seronegative patients (89–91). These HIV-seronegative patients who are KSHV-infected tend to experience a worse clinical prognosis; their disease is frequently complicated by autoimmune hemolytic anemia and polyclonal gammopathies (92).

In MCD, KSHV is present in cells belonging to the B cell lineage. A subset of these cells have a centroblastic/immunoblastic morphology and have been termed plasmablasts by Dupin et al. They are not present in KSHV-negative MCD (92, 93).

KSHV-positive MCD is therefore a distinct disease entity and has been designated as a plasmablastic variant of MCD (93). The rearranged heavy-chain-variable regions of the KSHV-positive plasmablasts are not mutated, implying that these infected cells originate from naive B cells (M Du, unpublished). Their mature phenotype may result from KSHV infection, possibly because of expression of vIL-6 rather than from a germinal center reaction.

KSHV GENES AND DISEASE PATHOGENESIS

A newly recognized feature of some DNA viruses, and in particular herpesviruses and poxviruses, is the piracy and incorporation of host cell genes into their viral genomes (94). KSHV encodes homologs of human cyclin D (vCYC, ORF72) (95), an IL-8-like G-protein coupled receptor (vGPCR, ORF74) (96), three chemokine homologs, vMIP-I, vMIP-II and vMIP-III (ORFs K6, K4, K4.1) (16, 17, 94), a homolog of IL-6 (ORF K2) (17, 94, 97), two ORFs with some sequence similarity to interferon regulatory factors (vIRFs, ORFs K9 and K10.5) (94), a new member of the virus encoded family of FLICE inhibitory proteins (vFLIP, ORF13) (98, 99), and a bcl-2 homolog (ORF16) (100, 101). In addition, KSHV encodes genes similar to the complement-binding proteins CD21/CR2 (ORF4) and an NCAM-like adhesion protein (ORF14) (16). Presumably, all of these genes help the virus to survive and replicate successfully in its host.

KSHV v-Cyclin

Cellular cyclins regulate cell proliferation and cell cycle progression (102, 103). The G1 cyclins D and E accelerate transit through the G1 phase of the cell cycle into the S phase and therefore commit cells to a further cycle of DNA synthesis. The aberrant expression of cellular D-type cyclins is strongly implicated in the pathogenesis of various malignancies (104, 105). All cyclins function by associating with cyclin-dependent kinases (CDKs) to phosphorylate and inactivate cell cycle checkpoint molecules. The cyclin encoded by KSHV (vCYC) associates predominantly with CDK6, and this complex can phosphorylate, and therefore inactivate, pRB (95, 106, 107). Like cellular cyclins, KSHV vCYC in concert with CDK6 can also activate cyclin A expression (108). Unlike cellular cyclins, KSHV vCYC-Cdk6 complexes are resistant to inhibition by the CDK inhibitors p16(Ink4a), p21Cip1, and p27Kip (109, 110). Although the protein expression of vCYC in KSHV-associated disorders still needs to be confirmed, this protein probably promotes cell cycle progression by a mechanism analogous to that of overexpressed cellular D-type cyclins.

KSHV G-Protein-Coupled Receptor

The KSHV G-protein coupled receptor (vGPCR, ORF74) encodes for a constitutively active receptor and is one of the potential oncogenes encoded by KSHV

(111). Cellular GPCRs that are constantly stimulated or that become constitutively active by mutation can transform cells and are involved in the pathogenesis of some human tumors (112). KSHV vGPCR is most homologous to the human receptors for IL-8 (CXCR-1 and CXCR-2) (96, 113), an endothelial cell chemokine and angiogenic factor. KSHV vGPCR activates the phosphoinositide pathway (a mitogenic signaling pathway) in COS-1 cells, and in vitro transfection of rat fibroblasts with KSHV vGPCR leads to cell proliferation (111). NIH3T3 cells expressing vGPCR form foci and induce tumors when injected into nude mice (114). Additionally, supernatants from cells transfected with vGPCR contain elevated levels of vascular endothelial growth factor (VEGF), which induces an angiogenic phenotype when applied to human umbilical-vein endothelial cells (114). Recently, Yang et al raised transgenic mice with vGPCR under T-cell promoter control. The expression of vGPCR in hematopoietic cells did not induce identifiable lymphoproliferation but resulted in the development of angioproliferative lesions in multiple organs that morphologically resemble KS lesions (115). This suggests that KSHV-GPCR signaling not only is linked to cellular proliferation and possible transformation but also could induce paracrine responses, such as angiogenesis, which may be relevant to KS pathogenesis.

KSHV vbcl-2

KSHV encodes a gene (ORF16) with sequence similarity to cellular bcl-2 (100, 101). The EBV and HVS genomes also each carry a bcl-2 homolog. Members of the bcl-2 family of genes regulate programmed cell death within a cell in either a pro-apoptotic or an anti-apoptotic manner by dimerization with other members of the family. Although the mechanism is poorly understood, the heterodimerization of cellular bcl-2 with bax is important in overcoming bax-mediated apoptosis (116). Whether KSHV-bcl-2 dimerizes with other bcl-2 family members in vivo is not yet clear; however, KSHV-bcl-2 can overcome bax-mediated apoptosis (100, 101). vbcl-2 transcripts are present predominantly in the lytic phase of viral replication (101, 117). This expression pattern, along with the homology between KSHV ORF16 and other members of the bcl-2 family, suggests that KSHV-bcl-2 might prolong the lifespan of virus-infected cells. Deregulated bcl-2 expression has been shown to occur in some human malignancies, such as follicular lymphomas (118, 119), suggesting that ectopic expression of KSHV-bcl-2 may also contribute to tumorigenesis through its anti-apoptotic effect.

KSHV Interleukin-6

The IL-6 protein encoded by KSHV (vIL-6) demonstrates sequence similarity to human IL-6, a cytokine that enhances B cell survival and proliferation, and is functional in preventing apoptosis of the IL-6-dependent mouse plasmacytoma cell line, B9 (94, 120). Immunohistochemical studies using polyclonal antibodies

specific for vIL-6 demonstrate that this viral cytokine is not expressed in the spindle cells of KS lesions (60, 94); however, in patients with KS, vIL-6 expression can be found in hemopoietic cells and in lymph nodes. vIL-6 is also expressed in PELs, cell lines derived from these lymphomas, and a subset of mantle-zone cells in KSHV-infected MCD lymph nodes (92). Like cellular IL-6, vIL-6 induces JAK1 phosphorylation and STAT1/STAT3 DNA binding activity. Human IL-6 also uses this pathway after associating with the human IL-6 receptor complex, composed of an IL-6R α subunit that binds the cytokine ligand and a gp130 subunit that transduces the cytokine signal across the cell membrane.

Although identical pathway signaling is employed by both vIL-6 and human IL-6 (121), important differences in receptor recognition exist (122, 123). Monoclonal antibody and polyclonal antisera directed against the IL-6R α receptor subunit failed to abolish vIL-6 activity, whereas antisera to gp130 blocked STAT induction (122). NIH3T3 stably expressing vIL-6 and injected into athymic mice resulted in increased multilineage hematopoiesis as well as angiogenesis mediated through VEGF (124).

Utilization of preexisting IL-6 signaling pathways appears to be a strategy employed by KSHV (as well as EBV) in infected hematolymphoid cells to promote cell survival and prevent apoptosis. It leads to plausible pathogenic mechanisms for disease association involving lymphoproliferative disorders.

KSHV FLICE-Inhibitory Proteins

A new family of viral inhibitors, the vFLIPs (for FLICE-inhibitory proteins), has recently been identified. The vFLIPs interfere with apoptosis signaled through death receptors. vFLIPs are present in several gammaherpesviruses (including KSHV ORF13), as well as the oncogenic human molluscipoxvirus 1 (98, 99). Cells expressing vFLIPs are protected against apoptosis induced by CD95 or by tumor necrosis factor receptor-1 (TNFR-1) (98, 99). Interestingly, all FLIP-encoding gammaherpesviruses also have a bcl-2 homolog. These viruses may therefore exploit two complementary anti-apoptotic pathways provided by a bcl-2 homolog and a vFLIP.

KSHV Interferon Regulating Factor

For the gammaherpesviruses, like all other herpesviruses, the ability to evade host immune defenses is critical to survival. KSHV encodes a gene, KSHV vIRF (ORF K9), which has low but significant sequence similarity to the interferon regulating factor (IRF) family of proteins (94). IRFs are transcriptional factors involved in transducing or modifying interferon signal transduction to specific interferon-responsive genes by binding to interferon-stimulated response elements (ISREs) in their promoters (125). Two members of this family, human IRF-1 (huIRF-1) and huIRF-2, are antagonistic to each other in their effector functions (126). vIRF appears to share functional homology with huIRF-2, which is known

to be a repressor of interferon-induced gene transcription because vIRF can inhibit interferon signaling as measured by reporter assays (127–129). In vIRF, unlike its human counterpart, no evidence of direct binding to DNA has been experimentally demonstrated.

Human IRF-2 has also been shown to have oncogenic activity in NIH3T3 cells, which can be reversed by IRF-1 overexpression (126). Likewise, vIRF can transform NIH3T3 cells, causing focus formation and tumor in nude mice (127). This viral gene therefore not only apparently contributes to the escape of virus-infected cells from immunosurveillance but also is another potential oncogene involved in KSHV tumorigenicity.

KSHV Latent Proteins Without Known Cellular Homologs

At the far right-hand end of the KSHV genome, the ORF K15 encodes a putative latent transmembrane protein in the same genomic location as EBV's *LMP2A* (19, 130). K15 has various splice mRNA transcripts, which are predicted to translate into proteins consisting of 4 to 12 transmembrane-spanning domains. Two highly divergent forms of K15, the predominant (P) and minor (M) forms, have been identified. These two alleles have only 33% amino acid homology to each other yet retain the 12 transmembrane-spanning domains and a cytoplasmic signal-transducing carboxyl terminus (C terminus). The cytoplasmic domain of K15, like *LMP2A* of EBV, has signaling motifs including potential SH2 and SH3 binding sites. K15 appears to be constitutively tyrosine-phosphorylated within a YEEVL motif in the C terminus. Like *LMP2A*, K15 modulates B cell receptor signal transduction, but the mechanism(s) appears to be distinct from that of *LMP2A* and does not involve the mobilization of intracellular free calcium. In addition, a putative TRAF binding site is present at the C terminus of K15. K15 induces NF- κ B activation, and this activity localizes within the last 18 amino acids of K15, which contains the putative TRAF binding motif (T Sharp, C Boshoff, unpublished). Between the P and M forms of K15, the last 18 amino acids are conserved for both the putative TRAF binding and the SH2 (YEEVL) binding motifs. Like *LMP1*, K15 is also able to activate JNK. This ability to activate JNK, like that of NF- κ B activation, is located within the last 18 amino acids of the K15 extreme C terminus. The JNK signaling pathway is known to lead to the activation of AP-1, a pleiotropic transcription factor implicated in cellular transformation and phenotypic changes.

Open reading frame 73 (ORF73) encodes the major immunogenic latency-associated nuclear antigen (LNA or LANA) of KSHV (131–133). LANA is expressed in all tumor cells of KSHV-related malignancies. LANA has been shown to maintain the KSHV episome and, via histone H1, tethers the viral genome to chromatin during mitosis (134, 135). In addition, LANA interacts with the tumor suppressor protein p53 and represses its transcriptional activity (136). LANA therefore appears essential for KSHV persistence and might be an important transcription factor used by KSHV to transform cells.

KSHV: A New DNA Tumor Virus

The array of genes encoded by KSHV, some unique to it and others shared only among the rhadinoviruses, has provided hints and directions in dissecting out the mechanisms of viral pathogenesis and oncogenesis. Investigation of these genes has begun to demonstrate their functional activity in cellular signaling and regulatory pathways. Candidate oncogenes have been identified that may cause dysregulated proliferation or interfere with established tumor suppressor pathways.

Epidemiologic evidence is overwhelming in support of KSHV as the central factor in the development of KS, the most common AIDS-related malignancy. KSHV is also associated with body-cavity-based primary effusion lymphomas and therefore likely to be a new oncogenic DNA tumor virus.

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