expert reviews in molecular medicine

Kaposi's sarcoma: the role of HHV-8 and HIV-1 in pathogenesis

Kimberly E. Foreman

Kaposi's sarcoma (KS) is the most common neoplasm in acquired immune deficiency syndrome (AIDS) patients, with up to 20% of individuals infected with human immunodeficiency virus 1 (HIV-1) afflicted with this multifocal, systemic disease. For many years, scientists have striven to understand the complex pathogenesis of KS. Although experts generally agree on several key points [such as human herpesvirus 8 (HHV-8) being necessary but not sufficient for the development of KS], many questions still remain unanswered. This review summarises current theories on the molecular pathogenesis of KS, including the role of HHV-8, HIV-related proteins and growth factors in the initiation and progression of AIDS-related KS.

Kaposi's sarcoma (KS) is a multicellular, mesenchymal neoplasm characterised by the presence of spindle-shaped tumour cells, angiogenesis, extravasated erythrocytes, oedema and a mononuclear inflammatory cell infiltrate (Fig. 1) (reviewed in Ref. 1). Prior to the AIDS (acquired immune deficiency syndrome) epidemic, KS was considered a relatively rare, benign disease, occurring primarily in elderly men of Mediterranean and Eastern European descent (classical KS). These patients typically present with reddish-brown to brown-violet plaques or nodules on the skin of the hands and feet. Although these lesions can cause considerable pain, particularly in areas with oedema, the disease is seldom life threatening. Unlike classical KS, endemic KS occurs mainly in children and young adults in sub-Saharan Africa. This form of KS often presents with lymphadenopathy rather than cutaneous lesions and has a poor prognosis. KS is also known to occur in immunosuppressed organ-transplant patients, particularly renal-transplant recipients (iatrogenic KS). Lesions in these patients are generally limited to the skin and oral mucosa, and typically regress with discontinuation of immunosuppressive therapy.

The AIDS-associated form of KS (epidemic KS or AIDS-KS) was first recognised in 1981 by dermatologists in New York City and San Francisco, USA who began to see cutaneous KS lesions in otherwise healthy young homosexual males (Ref. 2). As the AIDS epidemic spread, KS became the most common neoplasm in patients infected with human immunodeficiency virus 1 (HIV-1) and was recognised as an AIDS-defining illness. AIDS-KS is widely regarded as more aggressive, disseminated and resistant to treatment than all other forms of KS, including those also associated with immunosuppression. In HIV^+ patients, KS lesions are widespread in the skin and often involve the internal organs, particularly the lungs and gastrointestinal tract

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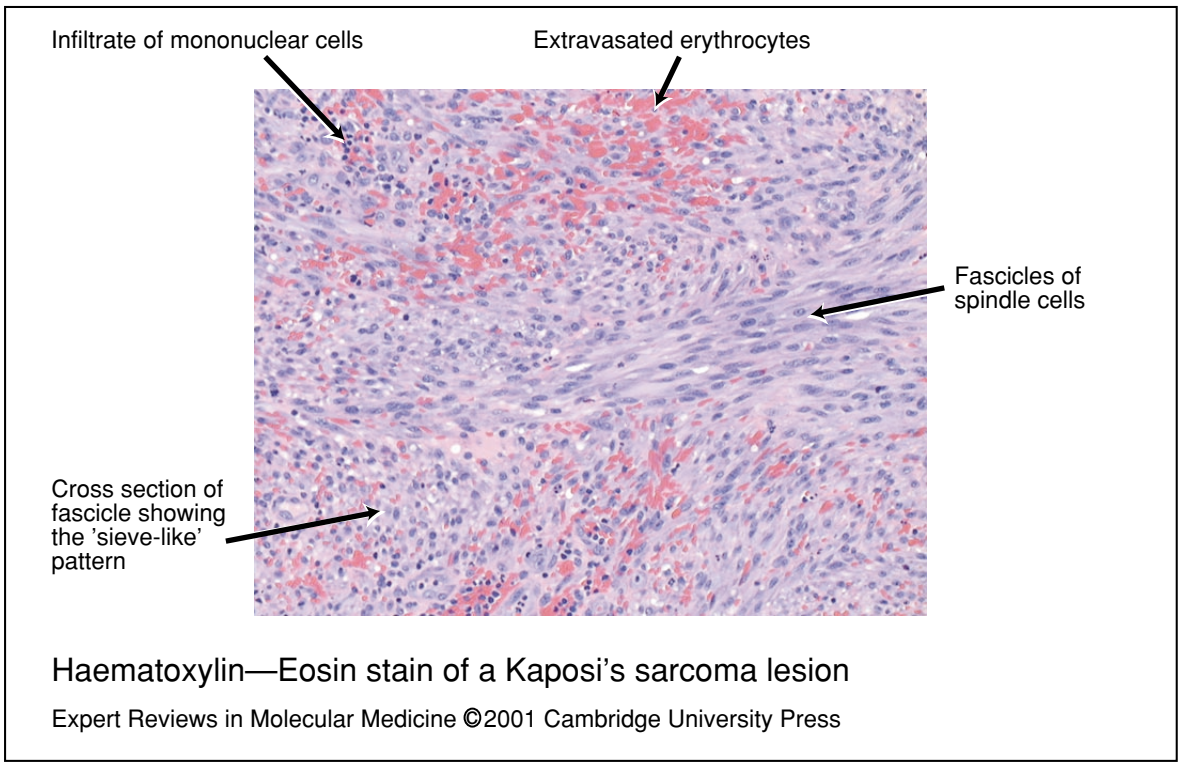

Figure 1. Haematoxylin–Eosin stain of a Kaposi's sarcoma lesion. Histologically, Kaposi's sarcoma is characterised by fascicles of spindle-shaped tumour cells, angiogenesis, extravasated erythrocytes, oedema and an infiltrate of mononuclear inflammatory cells **(fig001kfm)**.

(Ref. 3). The prognosis is poor, with approximately 12% of AIDS-KS patients dying as a result of complications related to KS and the remaining patients suffering significant morbidity. The incidence of KS has decreased significantly in recent years owing to the advent of highly active antiretroviral therapy (HAART) (Ref. 4). However, failure of HAART occurs in over 50% of treated patients and, even in patients with undetectable HIV viral loads, KS can recur and progress (Refs 5, 6).

This review summarises current theories on the molecular pathogenesis of KS with respect to the role of human herpesvirus 8 (HHV-8), HIV-1-related proteins (particularly Tat protein), and cytokines and growth factors in the initiation and progression of AIDS-KS. In addition, the need to develop an appropriate model system in which to study KS pathogenesis is discussed.

HHV-8 and AIDS-KS

Evidence for HHV-8 as the aetiological agent of KS

Despite extensive clinical and epidemiological differences, all four forms of KS are histologically indistinguishable – a finding that suggests a common mechanism of pathogenesis. It has long been suspected that an infectious agent is the cause of KS (Ref. 7). In 1994, Chang, Moore and colleagues reported the presence of herpesvirus-like DNA sequences in lesional tissue from AIDS-KS patients that showed striking homology to Epstein–Barr virus (EBV) and herpesvirus saimiri (HVS) (Ref. 8). Subsequent work has confirmed these findings and has identified HHV-8 (also known as KS-associated herpesvirus, KSHV) as the first member of the γ2-herpesvirus family (genus *Rhadinovirus*) known to infect humans (Ref. 9). HHV-8 shares several features with other herpesviruses, including a large double-stranded DNA genome [approximately 165 kilobases (kb)], replication within the nucleus, and the ability to establish a stable latent infection within its natural host cell (reviewed in Refs 10, 11). Indeed, HHV-8 persists in latently infected cells as an episome during which time only a small subset of viral genes are expressed (Refs 12, 13). During reactivation (lytic cycle replication), the virus produces linear forms of the genome for packaging into progeny virions, and the lytically

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infected cell is ultimately destroyed. In addition to KS, HHV-8 has been consistently associated with two AIDS-associated lymphoproliferative disorders: primary effusion lymphoma (PEL) and a subset of multicentric Castleman's disease (MCD) (reviewed in Ref. 10).

Strong evidence exists to support the conclusion that HHV-8 is necessary for the development of KS. First, HHV-8 DNA has been detected in virtually all KS lesions. The virus has been consistently identified in all four epidemiological forms of KS and in all stages of the disease (early patch-stage lesions, plaques and late-stage tumour nodules) (Refs 14, 15, 16, 17). Second, seroepidemiological studies have found that the majority of KS patients (80–100%) have specific antibodies to HHV-8. Unlike other herpesviruses, HHV-8 does not appear to be ubiquitous, as very low seropositivity rates are found among normal or low-risk groups. However, seropositivity rates are dramatically increased in populations at higher risk for developing KS, such as HIV^+ homosexual males and individuals from Africa or southern Italy (Refs 18, 19). Finally, seropositivity or detection of HHV-8 genomic DNA has been shown to predict future development of KS (Refs 20, 21). Separately, these findings do not establish causation; however, taken together, they provide strong evidence that HHV-8 is indeed the aetiological agent of KS.

How does HHV-8 cause KS?

To date, there is no clear evidence indicating how HHV-8 might initiate/promote development of KS lesions. Two scenarios can be considered based on our current knowledge: (1) HHV-8 might play a crucial role in creating the necessary microenvironment for lesion development through autocrine/paracrine mechanisms; or (2) HHV-8 might directly transform cells, resulting in KS. These scenarios are not necessarily mutually exclusive. It has been postulated that KS begins as a hyperplastic proliferation mediated by growth factors and angiogenic factors, which, under certain conditions, becomes a true malignancy as the disease progresses (reviewed in Ref. 22). Therefore, it is plausible that KS progenitor cells (thought to be of endothelial cell origin) become activated following exposure to inflammatory cytokines and angiogenic factors. These activated cells might then be susceptible to HHV-8 infection and, once infected, produce/release viral proteins and/or a unique combination of host cellular factors that promote the growth and survival of both the infected and uninfected KS cells. Indeed, studies indicate that only a small portion (10%) of the spindle cells in early lesions appear to be infected with HHV-8 but, as the disease progresses, virtually all the KS cells become infected (Refs 23, 24). Transformation of the cells might occur at the later stages of the disease, resulting in a monoclonal proliferation, although this does not appear necessary.

This model of KS pathogenesis is in keeping with experimental evidence. Cesarman and colleagues recently demonstrated that infection of cultured bone-marrow-derived endothelial cells with HHV-8 results in cellular transformation, as determined by long-term proliferation, survival, telomerase activity and anchorage-independent growth (Ref. 25). However, only 1–6% of the cells in culture were infected with virus, indicating that paracrine mechanisms were responsible for the extended survival of the uninfected cells in the culture (Ref. 25). In addition, it is still debated whether KS is a true malignancy or a hyperplastic proliferation. Clonality studies evaluating the inactivation pattern of X chromosomes have yielded conflicting results, but a recent study by Gill et al. demonstrated that individual KS patients can develop both monoclonal and polyclonal lesions, and individual monoclonal lesions can contain different inactivation patterns (Refs 26, 27, 28). These results indicate KS lesions probably begin as a polyclonal proliferative process with the prospect of some lesions eventually arising from distinct transformed cells, resulting in a clonal tumour.

HHV-8 genes and the pathogenesis of KS

One striking feature of the HHV-8 genome is the large number of unique genes encoding homologues of human cellular proteins (Fig. 2). Recent studies have identified many of these viral homologues as biologically active proteins that can modulate growth, differentiation and cell survival, indicating they might play a role in the autocrine/paracrine stimulation of KS tumour cells or be directly responsible for cellular transformation. Table 1 summarises some of the HHV-8 genes that have been implicated in the pathogenesis of KS, and several excellent review articles have detailed descriptions of their individual functions (reviewed in Refs 10, 11).

Of particular interest to the pathogenesis of KS are viral homologues of human oncoproteins, and

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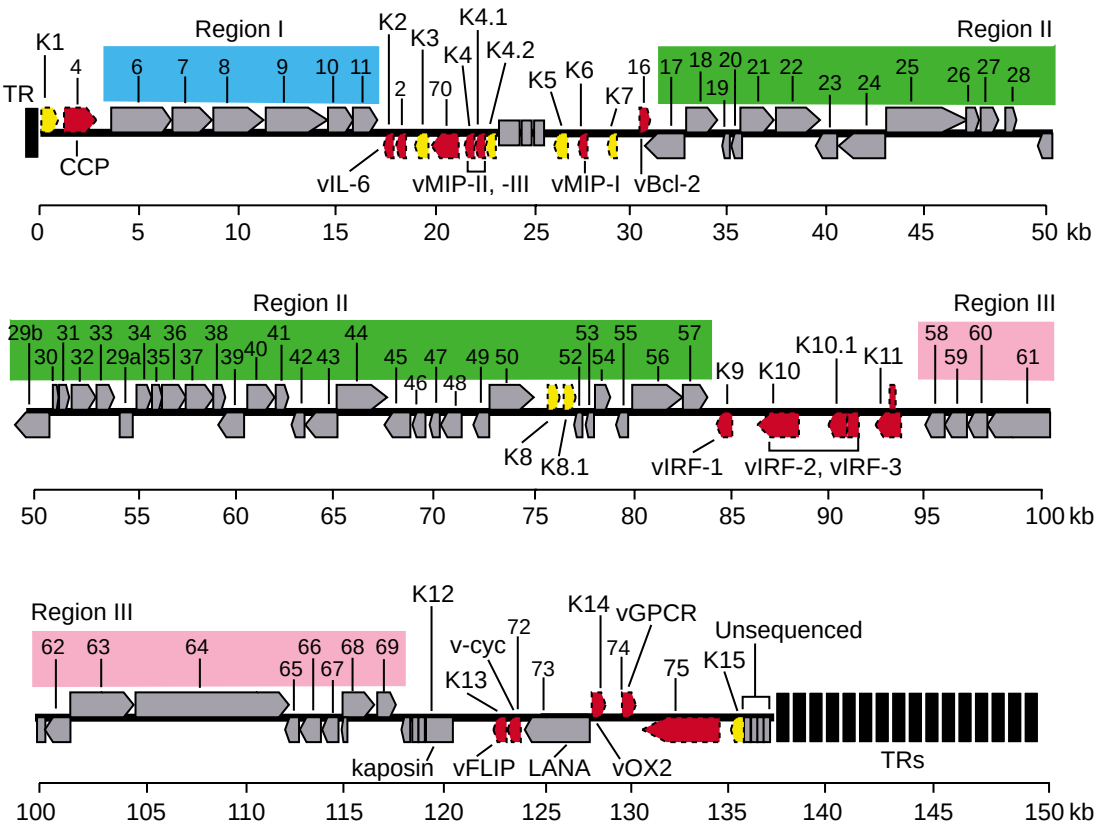

The human herpesvirus 8 (HHV-8) genome

Figure 2. The human herpesvirus 8 (HHV-8) genome. The genome consists of a long unique region (140.5 kb) encoding for over 80 open reading frames (ORFs), surrounded by terminal repeat regions (TRs) consisting of 801 base pair direct repeat units with a high G+C content. The ORFs are named after the corresponding genes in herpesvirus saimiri, and genes without significant homology are given the designation 'K'. Three large regions (I, II and III) contain genes conserved among the *Rhadinoviruses*, whereas the regions between them contain unique genes. Many of these unique genes encode homologues for host cellular proteins (shown in red with dotted outlines; genes without known homologues are shown in yellow with dotted outlines). Genes that are potentially important in the pathogenesis of KS are labelled. The figure is adapted from Ref. 108. Abbreviations: CCP, complement control protein; v-cyc, viral D-type cyclin; vFLIP, viral FLICE inhibitory protein; vGPCR, viral G-protein-coupled receptor; vIL-6, viral interleukin 6; vIRF, viral interferon regulatory factor; kb, kilobase; LANA, latency-associated nuclear antigen; vMIP, viral macrophage inflammatory protein **(fig002kfm)**.

angiogenic factors. HHV-8 viral cyclin D inactivates the retinoblastoma protein (pRb), which normally controls progression through the G1 cell cycle checkpoint (reviewed in Refs 29, 30). LANA (latency-associated nuclear antigen) interacts with and inactivates p53, a potent transcriptional regulator of cell growth (Ref. 31). Thus, HHV-8 encodes two proteins that independently inhibit the activity of two key tumour suppressor proteins and might help the virally infected cells circumvent normal cellular antiviral mechanisms. In addition, HHV-8 encodes two proteins – viral FLIP (FLICE inhibitory protein) and viral Bcl-2 – that have been shown to inhibit apoptosis (Refs 32, 33, 34). With respect to angiogenesis, HHV-8 viral macrophage inflammatory proteins (vMIP-I, -II and -III) are homologues of human CC chemokines, and have been shown not only to function as chemotactic

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Table 1. Human herpesvirus 8 (HHV-8) genes potentially involved in the development of Kaposi's sarcoma (KS) (tab001kfm)

HHV-8 gene	HHV-8 protein	Expression in KS	Predicted functional properties	Transforming potential
K1	K1 protein	Lytically infected cells?	Signalling, cellular growth	Yes (Ref. 100)
K2	vIL-6	No evidence	Cytokine, cellular growth	Unknown
K4/4.1	vMIP-II, -III	Lytically infected cells?	Chemokine, angiogenesis	No (Ref. 100)
K6	vMIP-I	Lytically infected cells?	Chemokine, angiogenesis	No (Ref. 100)
K9/10	vIRF	No evidence	Inhibition of IFN signalling	Yes (Ref. 101)
K12	Kaposin A, B and C	Latently infected cells	Unknown function	Yes (Ref. 102)
K13	vFLIP	Latently infected cells	Inhibition of apoptosis	Unknown
K14	vOX2	Unknown	Cell–cell interactions	Unknown
K15	–	Unknown	Contains a TRAF-binding motif similar to EBV LMP-1	Unknown
ORF4	–	Lytically infected cells?	Complement control protein	Unknown
ORF16	vBcl-2	Lytically infected cells?	Inhibition of apoptosis	Unknown
ORF72	v-cyc	Latently infected cells	Cell-cycle control	No (Ref. 10)
ORF73	LANA	Latently infected cells	Cell-cycle control and episomal persistence	Unknown
ORF74	vGPCR	Latently infected cells	Cellular growth, paracrine stimulation of factors needed to maintain KS	Yes (Ref. 40)

Abbreviations: v-cyc, viral D-type cyclin; EBV, Epstein–Barr virus; vFLIP, viral FLICE inhibitory protein; vGPCR, viral G-protein-coupled receptor; IFN, interferon; vIL-6, viral interleukin 6; vIRF, viral interferon regulatory factor; LANA, latency-associated nuclear antigen; LMP-1, latent membrane protein 1; vMIP, viral macrophage inflammatory protein; TRAF, tumour necrosis factor receptor-associated factor.

factors, but also to block binding of HIV-1 to chemokine receptors and to promote angiogenesis in chicken chorioallantoic membrane assays (Refs 35, 36, 37). Angiogenic responses to vMIPs are significantly higher than to cellular chemokines (for which no angiogenic activity has been described), and were only four- to fivefold less than those seen with vascular endothelial cell growth factor (VEGF) or basic fibroblast growth factor (bFGF) (Refs 38, 39). These proteins might, therefore, play an important role not only in recruiting inflammatory cells, but also in contributing to the neoangiogenesis seen in KS lesions. In addition, the HHV-8 G-protein-coupled receptor (vGPCR), a homologue of human GPCR, is a constitutively active receptor that can induce VEGF secretion (Ref. 40). Recent studies by Yang et al. demonstrate that transgenic mice expressing vGPCR develop erythematous lesions that eventually progress into KS-like lesions (Ref. 41).

Although these viral genes/proteins have the potential to contribute to the initiation or progression of KS by altering normal cellular functions, it is important to determine whether they are expressed in HHV-8-related tumours and how their expression is regulated. Preliminary evidence indicates that there might be important differences in regulation of HHV-8 gene expression in KS, PEL and MCD. For example, viral interleukin 6 (vIL-6)

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is constitutively expressed at low levels in PEL cell lines, and has been detected at both the mRNA and protein level in PEL biopsies and MCD; however, there is no evidence of vIL-6 expression in KS lesions (Refs 42, 43). Thus, this viral protein might play a unique role in the pathogenesis of PEL and MCD, but not in KS (Ref. 42). Furthermore, localisation studies have demonstrated that a majority of KS cells are latently infected with HHV-8, and that only a small portion of the tumour cells are undergoing lytic cycle replication (Ref. 44). Therefore, viral proteins expressed during either the latent or the lytic cycle might be important in the paracrine stimulation of the cells within the tumour, whereas only proteins produced during latency are likely to be responsible for cellular transformation.

HIV-1 and AIDS-KS

Current evidence suggests that HHV-8 infection is necessary, but not sufficient, for the development of KS. Indeed, HHV-8 infection alone cannot explain the different clinical forms of KS, the aggressive nature of AIDS-KS, or the prevalence of the disease in men but not women. Additional co-factors, such as hormones, genetic predisposition and/or co-infection with other infectious agents, appear to be necessary for disease development. Although HIV-1 infection is clearly not required for the development of KS, HIV-1 is thought to play an important role in the pathogenesis of AIDS-KS, particularly in explaining the unusually aggressive behaviour of this form of the disease. Studies have shown that KS cells themselves are not infected with HIV-1; therefore, it is widely accepted that HIV-1 does not play a direct oncogenic role in AIDS-KS (Ref. 45). However, the precise role of HIV-1 in AIDS-KS is still not completely understood, and there is considerable debate over whether HIV-1 plays a passive role (through the induction of immunosuppression) or a more direct role in the pathogenesis of this disease.

Role of HIV-1 in AIDS-KS

Epidemiological and experimental evidence indicate that immunosuppression alone is unlikely to explain the role of HIV-1 in AIDS-KS. First, there is an overwhelming prevalence of KS in AIDS patients compared with other immunosuppressed patient populations. The relative risk of developing KS in AIDS is 70-fold higher than that for other immunosuppressed patient groups (Ref. 46). Second, KS is considered an AIDS-defining illness and frequently occurs early in AIDS prior to the onset of severe immunosuppression (Refs 47, 48). Finally, there is an overwhelming association of KS with HIV-1, but not HIV-2, infection (Ref. 49). HIV-1 and HIV-2 are related, yet distinct, retroviruses, with only 40% identity between their genomes (Refs 50, 51). Recent studies by Ariyoshi et al. demonstrated that KS developed almost exclusively in patients infected with HIV-1, but not HIV-2, in Gambia, West Africa, despite essentially equivalent seroprevalence for HHV-8 and severity of immunosuppression (late-stage disease) in both groups (Ref. 49).

A larger, more direct role for HIV-1 in AIDS-KS pathogenesis has been proposed in which HIV-1 promotes the initiation and progression of KS through at least two crucial paracrine mechanisms: (1) by production of the Tat protein and (2) by promoting cytokine production (reviewed in Ref. 22). It is well recognised that cytokines are essential for the growth and proliferation of KS tumour cells, and HIV-1-infected cells have been shown to produce a variety of inflammatory cytokines that stimulate KS tumour cell growth (Ref. 52). Both of these aspects are discussed in more detail below.

Role of the HIV-1 Tat protein in AIDS-KS

For several years, studies have focused on a potential role for the HIV-1 Tat protein in KS. Tat is an 86 amino acid protein that specifically binds to the stem–loop structure at the 5' end of the viral RNA known as TAR (Tat activation region), resulting in a 10–100-fold increase in HIV-1 mRNA production (Fig. 3) (reviewed in Refs 53, 54). It is believed that the primary function of Tat is to increase the processivity of RNA polymerase II (which allows synthesis of full-length transcripts) and to increase transcription initiation.

In addition to HIV-1-infected cells producing Tat intracellularly to facilitate HIV-1 viral replication, they release soluble Tat protein, which is able to act in trans on uninfected cells (Refs 55, 56). Once inside a cell, this Tat protein might directly interact with cellular genes to alter their expression. Tat has been shown to increase expression of the gene encoding tumour necrosis factor β (TNF-β), but not of the genes encoding IL-1 and IL-6 in in vitro systems (reviewed in Ref. 57). This increase might be due to the interaction of Tat with the AUCUC sequence in the TNF-β promoter as it is similar to the sequence within

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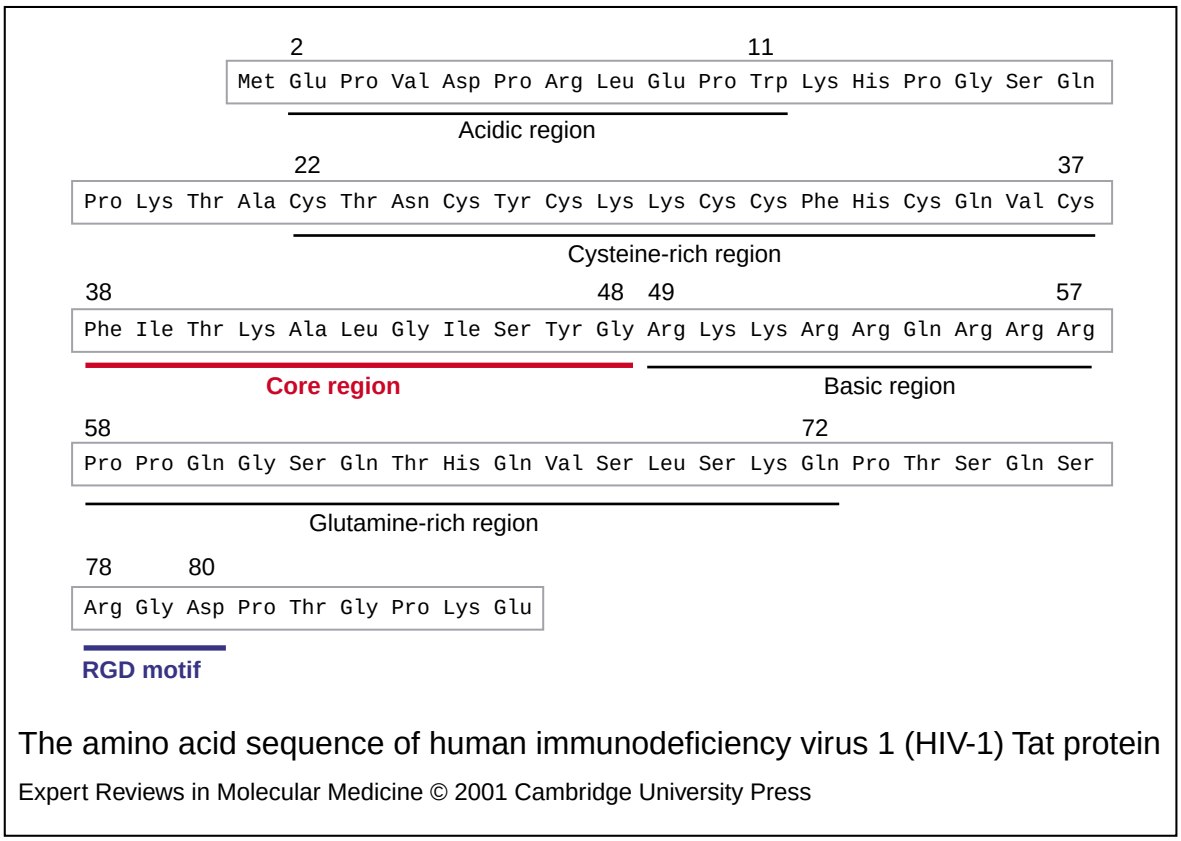

Figure 3. The amino acid sequence of human immunodeficiency virus 1 (HIV-1) Tat protein. The amino acid sequence is based on human immunodeficiency virus 1 (HIV-1) isolate BH10 (GenBank accession number M15654). Tat protein contains many interesting structural features; for example, previous studies have shown that the core region is crucial for activation of HIV-1 transcription, the basic region is essential for binding to TAR (Tat activation region) and functions as a nuclear/nucleolar targeting signal, and the cysteine-rich region may mediate dimerisation, although the significance of this is unclear. The highly conserved Arg-Gly-Asp (RGD) sequence in the C-terminus is thought to be important in binding to integrins (Ref. 54) **(fig003kfm)**.

TAR that is recognised by Tat (AUCUG) (Ref. 58). Soluble Tat can also bind to both $\alpha_v\beta_3$ and $\alpha_5\beta_1$ integrins. Integrins are receptors for extracellular matrix proteins that are crucial for endothelial cell adhesion, migration and invasion. Tat competes with natural integrin ligands to bind to $\alpha_v\beta_3$ and $\alpha_5\beta_1$ through a highly conserved Arg-Gly-Asp (RGD) sequence in the C-terminus (Fig. 3), and this interaction might function to induce intracellular signals that ultimately lead to changes in gene expression (Ref. 59).

Studies have revealed a variety of biological activities associated with the Tat protein (see Table 2 for a summary) that might be important in the pathogenesis of KS (Fig. 4). This is well illustrated in animal models including *tat*-transgenic mice, which develop skin lesions resembling KS (Ref. 60). A majority of *tat*-transgenic mice have skin abnormalities, and 15% of the animals eventually develop KS-like lesions. Interestingly, only male mice develop lesions, suggesting a possible hormonal influence (Ref. 60). In addition, injection of recombinant Tat protein into the skin of nude mice induces transient KS-like lesions, and injection of Tat in combination with bFGF results in a synergistic activity, producing lesions in a larger proportion of the animals (Ref. 61).

Cellular activation

Tat increases expression of cytokines, including TNF-β, IL-6, IL-2, IL-8 and IL-10, in T cells, peripheral blood mononuclear cells (PBMCs) and/or endothelial cells (Refs 62, 63, 64, 65, 66). These effects appear to be mediated by a variety of mechanisms including protein kinase C activation, NF-κB binding, and direct interaction of Tat with cellular promoters, which

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Table 2. Biological activities of human immunodeficiency virus 1 Tat protein potentially involved in the pathogenesis of Kaposi's sarcoma (tab002kfm)

Observed biological activity	Refs
Induction of cytokine and growth factor expression	62, 63, 64, 65
Induction of adhesion molecule expression	65, 69
Modulation of apoptosis	103, 104, 105
Induction of angiogenesis	73, 106
Promotion of growth and proliferation of Kaposi's sarcoma tumour cells	56, 68
Induction of chemotaxis	107
Induction of human herpesvirus 8 replication	76

ultimately results in the initiation of transcription (Refs 58, 63, 66, 67). In addition, extracellular Tat protein has been shown to activate normal endothelial cells as well as stimulate the growth, proliferation, adhesion and migration of KS tumour cells (Refs 56, 68). Tat protein not only induces cytokine production, but also induces the expression of cellular adhesion molecules. E-selectin, intercellular adhesion molecule 1 (ICAM-1) and vascular cell adhesion molecule 1 (VCAM-1) expression is increased on Tat-stimulated endothelial cells, and this expression can be further enhanced by cytokines (Refs 65, 69). Current evidence indicates that the effects of Tat on growth, proliferation and adhesion/migration of endothelial and KS cells are likely to be due to Tat interacting with integrins. Of interest, cytokines are also known to induce cellular responsiveness to Tat protein, due, in part, to induction of integrin expression.

Angiogenesis

Tat protein has been shown to have angiogenic properties both in vitro and in vivo. Extracellular Tat induces migration and invasion of cytokine-stimulated endothelial cells, and its activity is enhanced by heparin (Refs 70, 71). This is similar to other known angiogenic factors, such as bFGF, that are also heparin-binding proteins (Ref. 72). Recent studies have shown that Tat binds to and activates the tyrosine kinase receptor FLK-1/KDR, a known receptor for VEGF, and blockade of this receptor inhibits Tat-mediated angiogenesis (Refs 73, 74). In contrast, activation of endothelial cells by Tat does not occur through FLT-1, another VEGF tyrosine kinase receptor (Ref. 73). As the FLK-1/KDR receptor is expressed in KS, this might provide a mechanism by which Tat induces angiogenesis in this disease (Ref. 75). In addition, studies have demonstrated that cytokines increase expression of bFGF and VEGF; furthermore, bFGF, but not VEGF, can act synergistically with Tat to induce migration, adherence and growth of endothelial cells (Ref. 75). This effect appears to be related to $\alpha_v\beta_3$ expression, which might indicate that Tat not only interacts directly with VEGF receptors but might also induce angiogenesis through ligation of integrins.

Induction of HHV-8 replication

Studies are currently in progress to determine whether Tat protein plays a role in KS pathogenesis by interacting directly with HHV-8. Harrington et al. published a brief report indicating that HIV-1 Tat might induce lytic cycle replication of HHV-8 (Ref. 76). They suggest that treatment of HHV-8-infected PBMCs or PEL cell lines with Tat increased HHV-8 DNA; however, in-depth, confirmatory studies have yet to be published. Of interest, there is support for this idea in the literature, as HIV-1 Tat has been shown to enhance replication of HHV-6 (Ref. 77).

Cytokines and growth factors in AIDS-KS

The importance of cytokines in the pathogenesis of KS was originally demonstrated by Gallo, Ensoli and colleagues, who found that cytokines

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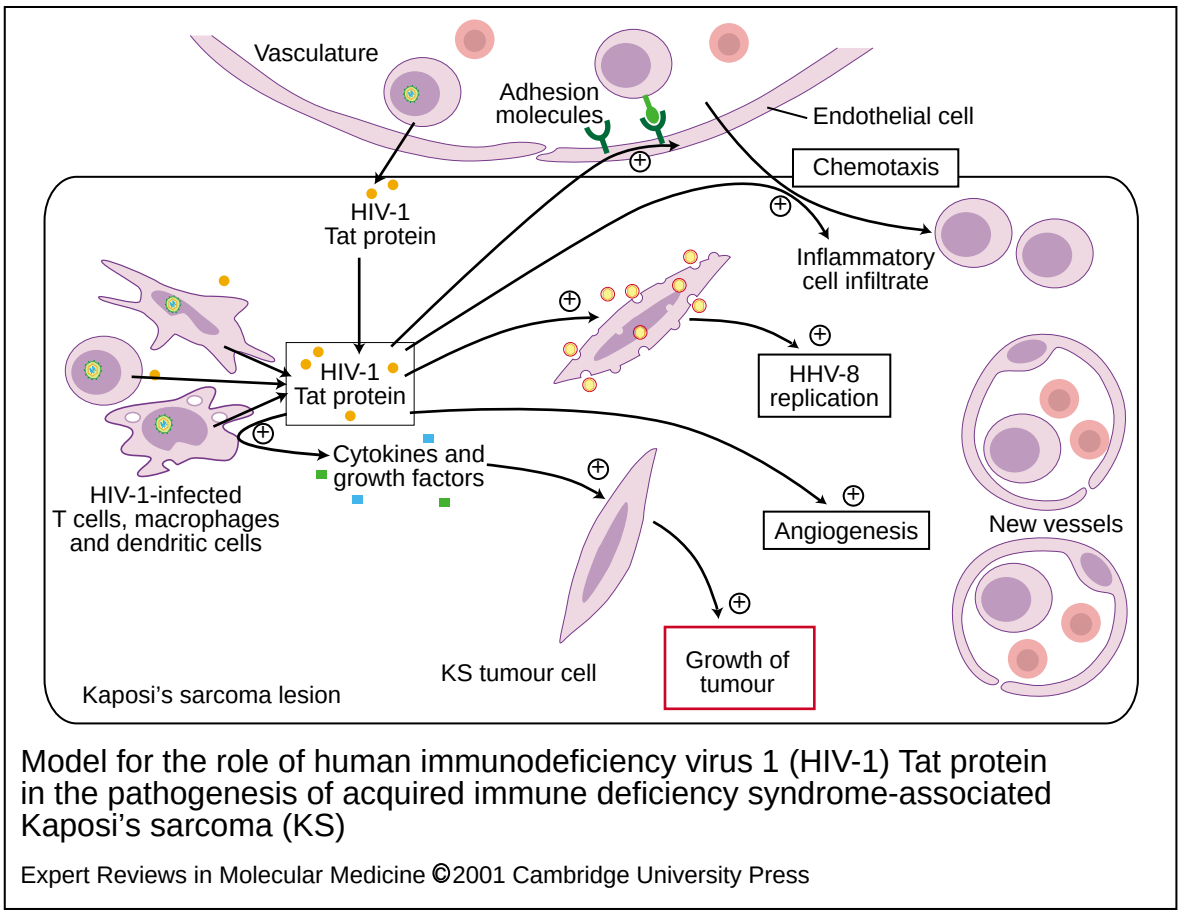

Model for the role of human immunodeficiency virus 1 (HIV-1) Tat protein in the pathogenesis of acquired immune deficiency syndrome-associated Kaposi's sarcoma (KS)

Figure 4. Model for the role of human immunodeficiency virus 1 (HIV-1) Tat protein in the pathogenesis of acquired immune deficiency syndrome-associated Kaposi's sarcoma (KS). HIV-1 Tat protein might be produced and released by HIV-1-infected cells (including T cells, monocyte/macrophages and dendritic cells) within the KS lesion. Tat protein might also be released by circulating HIV-1-infected cells and brought to the area via the vasculature within the lesion. Tat protein would then be available to stimulate cytokine and growth factor production, resulting in proliferation of the KS tumour cells. Tat might also induce adhesion molecule expression on endothelial cells, induce chemotaxis of immune cells into the lesion, promote angiogenesis, and/or directly interact with human herpesvirus 8 (HHV-8), resulting in reactivation of viral replication **(fig004kfm)**.

are essential to the growth of KS tumour cells in culture (Refs 52, 78). Since then, various investigators have shown that many cytokines are important in the pathogenesis of KS, including hepatocyte growth factor (scatter factor, HGF/SF), oncostatin M (OSM), IL-1β, TNF-α, interferon γ (IFN-γ), transforming growth factor β (TGF-β), granulocyte–macrophage colony-stimulating factor (GM-CSF), IL-6, bFGF and platelet-derived growth factor (PDGF) (reviewed in Refs 79, 80). These cytokines are produced by both autocrine and paracrine mechanisms within the KS lesion to create the necessary microenvironment for tumour initiation and progression.

Although it is difficult to determine the exact source of particular cytokines and growth factors within the KS lesion, clues can be gathered from the study of tumour cells from KS lesions in culture, HHV-8-infected B-cell lines, and HIV-1-infected T cells, monocytes/macrophages and dendritic cells. KS tumour cells in culture have been shown to produce and release biologically active cytokines, such as bFGF, IL-1β, PDGF, GM-CSF and IL-6. These cytokines not only act as autocrine growth factors, but also stimulate the proliferation of normal endothelial cells and induce angiogenesis. However, studies performed on isolated KS tumour cells might tell only part of the story as KS cells grown in culture do not appear to be infected with HHV-8 (except

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during early passages) (Ref. 81). It is currently unknown what effect, if any, HHV-8 infection has on cytokine production and secretion by these tumour cells in vivo. Studies using HHV-8-infected PEL cell lines indicate that these cells produce IL-6, OSM, HGF/SF and IL-10, in addition to HHV-8-encoded vIL-6 (Refs 82, 83). Although it is unclear whether circulating lymphocytes infected with HHV-8 produce a similar pattern of cytokines, HHV-8-infected B cells have been detected in approximately 50% of KS patients (Refs 20, 84). Finally, HIV-1-infected cells, including T cells, monocytes/macrophages and dendritic cells, have been shown to secrete inflammatory cytokines such as TNF-α and IL-1β, as well as induce the expression of cytokines by neighbouring, uninfected cells (Ref. 85). HIV-1-infected patients have been shown to have higher circulating levels of IL-1, IL-3, IL-4, IFN-γ, TNF-α, TNF-β, TGF-β and OSM, which is probably a result of chronic viral infection and stimulation of the immune system (Ref. 86).

In addition to their crucial role in the pathogenesis of KS through the induction of angiogenesis and proliferation of KS tumour cells, cytokines have been implicated in the induction of HHV-8 replication. A cytokine-driven increase in HHV-8 replication could be important in increasing local HHV-8 viral load and in promoting disease progression. Recent studies have shown that soluble factors produced by, or in response to, HIV-1-infected T cells induce HHV-8 replication and the production of progeny virions (Ref. 87). These studies have identified OSM, HGF/SF and IFN-γ, but not IL-6, IL-2 and TNF-α, as cytokines able to induce lytic cycle replication. Similar studies by other groups have also identified IFN-γ as a cytokine that induces HHV-8 replication, but have found no effect by TNF-α, IL-1, IL-2, IL-6, GM-CSF or bFGF (Refs 88, 89, 90).

A model of KS pathogenesis

The current model of the pathogenesis of AIDS-KS is summarised in Figure 5. This multistep model begins with cytokines and growth factors, produced by HIV-1-infected cells and/or activated mononuclear cells, playing a crucial role in disease initiation. Stimulation of KS progenitor cells by these cytokines and growth factors promotes their proliferation and activation, resulting in formation of a 'pre-KS' cell. The activated 'pre-KS' cells acquire the characteristic spindle-shaped morphology and probably begin to produce cytokines, which further promote their own growth and proliferation as well as promote angiogenesis and infiltration of inflammatory cells. In addition, the activation of the 'pre-KS' cells might induce expression of unique receptor(s) that are crucial for HHV-8 infection of these cells. HHV-8, which normally persists in host B cells, might be reactivated by stimulation with cytokines and/or HIV-1 Tat protein, resulting in the production of progeny virions. These virions can then infect the activated pre-KS cells. KS lesion formation might progress through a combination of continued cytokine stimulation (through both autocrine and paracrine mechanisms), production and release of HIV-1 Tat protein, and production of HHV-8-related proteins in the KS cells themselves. Each of these factors plays a unique role in inducing proliferation of KS cells and in blocking the apoptosis that would normally be induced by host antiviral immune responses. Cellular transformation might also occur in certain cases, through either persistent cellular activation or expression of HHV-8-associated proteins, resulting in clonal tumour formation. The combined influences of HIV-1 Tat protein, cytokine production in response to HIV-1 infection and immunosuppression are probably responsible for the more aggressive nature of AIDS-KS.

In other forms of KS, where HIV-1 infection does not occur, the source of initiating cytokines and immune system activation is unclear. It is likely that other factors, such as chronic infection by other agents, results in the correct microenvironment for formation of the pre-KS cell and infection by HHV-8. For example, the geographical areas associated with African (endemic) KS overlap areas with high incidence of EBV and *Plasmodium* infections. Therefore, the clinical course of KS in each individual patient is likely to be determined by a variety of factors, including the pattern of cytokine production, the presence of other infectious agents, genetic factors and immunological status.

Future directions

An ongoing problem in the study of KS has been the lack of an appropriate in vivo model system to study the disease. Isolated KS tumour cells have provided invaluable information regarding KS; however, studies have consistently shown that HHV-8 is lost from the cultures after a few passages (Ref. 81). Nevertheless, these cells can

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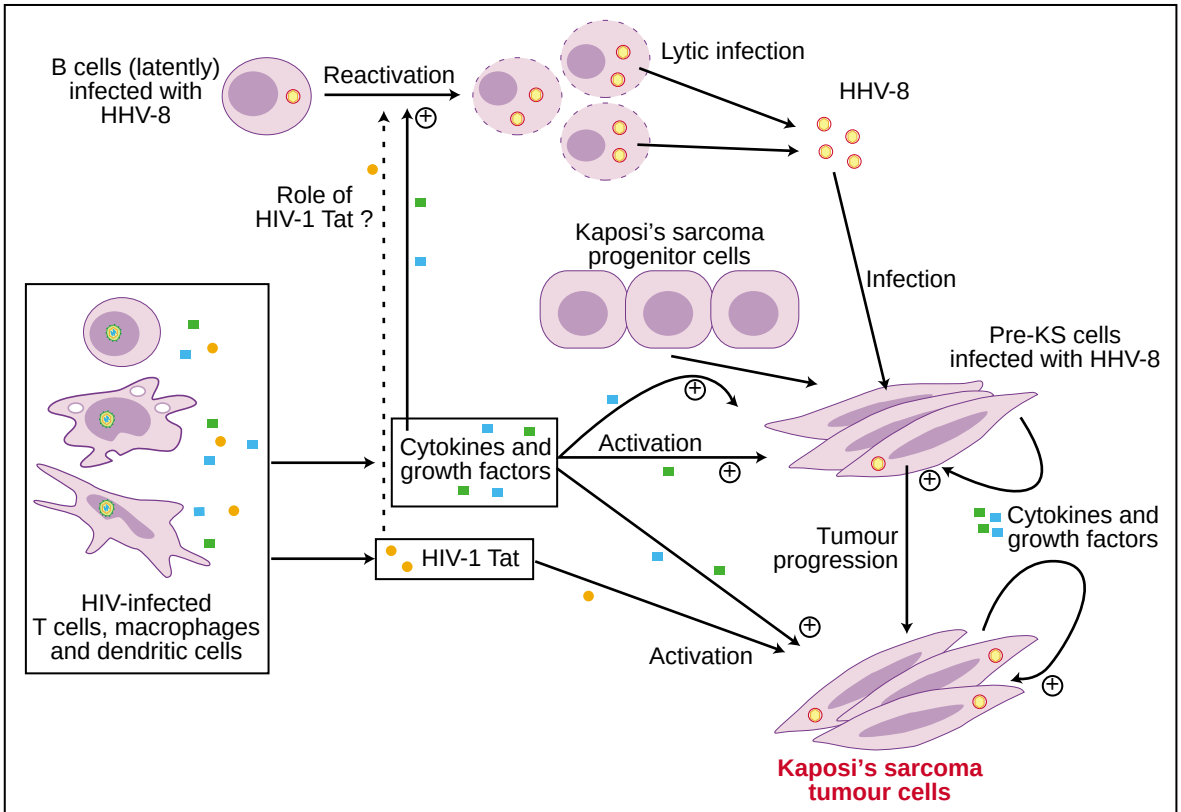

Figure 5. Model for the pathogenesis of acquired immune deficiency syndrome-associated Kaposi's sarcoma (KS). Cytokines and growth factors produced by human immunodeficiency virus 1 (HIV-1)-infected cells (or other activated immune cells) might stimulate the progenitors of the KS tumour cell. This stimulation might result in the activation and proliferation of these precursors, leading to the formation of a 'pre-KS' cell, which acquires the characteristic spindle-shaped morphology of the tumour cell and probably begins to produce autocrine cytokines and growth factors. Human herpesvirus 8 (HHV-8), which normally persists in B cells, might be reactivated by cytokines (solid arrow) and/or HIV-1 Tat protein (dashed arrow) resulting in the production of progeny virions and infection of the activated pre-KS cells. Tumour formation might then progress through a combination of continued cytokine stimulation (both autocrine and paracrine), production and release of HIV-1 Tat protein, and production of HHV-8-related proteins by the KS tumour cells themselves (not shown) **(fig005kfm).**

be injected into the skin of nude mice, resulting in a transient, angiogenic lesion resembling early KS (Ref. 91). Similar lesions are induced following injection of nude mice with conditioned media from KS cells, bFGF or HIV-1 Tat protein (Refs 61, 92, 93, 94). To date, only a few immortalised KS cell lines have been described, including the SLK and KSY-1 cell lines (Refs 95, 96). These cells, which are not infected with HHV-8, readily produce tumours when injected into nude mice (Ref. 95). Although these models lack HHV-8 infection, they are well-characterised, reproducible systems that can be used to study various aspects of KS including novel therapeutic approaches that do not directly target HHV-8 infection or replication.

Recent studies involving HHV-8 have also attempted to demonstrate production of either KS or lymphoproliferative diseases following expression of HHV-8-encoded proteins or infection with the virus. Dittmer et al. reported HHV-8 infection of $CD19^+$ B cells in severe combined immunodeficient (SCID) mice implanted with human fetal thymus and liver grafts (Ref. 97). HHV-

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8 infection was limited to the implant, and the animals did not develop KS-like lesions; however, the authors used this model to demonstrate that ganciclovir interferes with both establishment and maintenance of HHV-8 infection in $CD19^+$ B cells. These data confirmed and extended earlier studies looking at antiviral agents in experiments using PEL cell lines (Ref. 97).

In collaboration with Brian Nickoloff (Loyola University, Maywood, IL, USA), Jacques Friborg, Jr (Bristol-Myers Squibb Pharmaceuticals, Wallingford, CT, USA), Gary Nabel (National Institutes of Health, Bethesda, MD, USA) and others, my laboratory has recently attempted to develop a new model for KS using normal human skin engrafted on SCID mice. This well-characterised transplantation system results in a graft with clinical, histological and immunological characteristics that are remarkably similar to pre-transplanted skin (Ref. 98). Injection of this normal human skin graft with KS-derived cell-free HHV-8 results in a thickened, erythematous lesion after 16–18 weeks, a result not found in control mice injected with heat-killed HHV-8 preparations (Ref. 99). These lesions had characteristics consistent with KS, including the presence of angiogenesis, and spindle-shaped cells with morphological and phenotypic characteristics similar to KS tumour cells in vivo (Ref. 99). In addition, the spindle-shaped cells could be isolated from the lesion and grown in culture, and were found to be latently infected with HHV-8 as demonstrated by immunohistochemical staining for ORF73, reverse transcriptase–PCR and Southern blot analysis (Ref. 99). Of interest, only 60% of animals injected with KS-derived HHV-8 developed lesions. It is currently unclear if the lack of consistent lesion development is a result of genetic differences related to the human skin donor, differences in individual mice, or the absence of an additional co-factor that is necessary to induce KS-like lesions reproducibly. Ongoing studies are focused on determining what factors are necessary to produce KS-like lesions consistently in this model. Although still in development, this new model might complement and extend previous KS models for the study of disease pathogenesis as well as evaluation of new therapeutic agents.

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Further reading, resources and contacts

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Schulz, T.F. (1999) Epidemiology of Kaposi's sarcoma-associated herpesvirus/human herpesvirus 8. Adv Cancer Res 76, 121-160, PubMed ID: 99234723

Schulz, T.F. and Moore, P.S. (1999) Kaposi's sarcoma-associated herpesvirus: a new human tumor virus, but how? Trends Microbiol 7, 196-200, PubMed ID: 99284900

Murakami-Mori, K., Mori, S. and Bonavida, B. (2000) Molecular pathogenesis of AIDS-associated Kaposi's sarcoma: growth and apoptosis. Adv Cancer Res 78, 159-197, PubMed ID: 20015393

The Society of Investigative Dermatology is an organisation dedicated to the advancement of skin research, including Kaposi's sarcoma.
http://www.sidnet.org/

The International AIDS Malignancy Conference (sponsored by the National Cancer Institute) and The International Workshop on KSHV and Related Agents are excellent meetings for current research information on HHV-8/KSHV and Kaposi's sarcoma. Website for the AIDS Malignancy Conference is given below.
http://ctep.info.nih.gov/AIDSOncoResources/default.htm

Author's affiliation websites:

Department of Pathology at Loyola University Medical Center.
http://www.luhs.org/depts/path/index.htm

Cardinal Bernardin Cancer Center.
http://www.luhs.org/svcline/cancer/index.htm

Loyola University Medical Center.
http://www.luhs.org/index.htm

Features associated with this article

Tables

Table 1. Human herpesvirus 8 (HHV-8) genes potentially involved in the development of Kaposi's sarcoma (KS) (tab001kfm).
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Figure 5. Model for the pathogenesis of acquired immune deficiency syndrome-associated Kaposi's sarcoma (KS) (fig005kfm).

Citation details for this article

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