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Kaposi's sarcoma herpesvirus/ Human herpesvirus-8 (KSHV/ HHV8), and the oncogenesis of Kaposi's sarcoma

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Abstract

Kaposi's sarcoma (KS) is the most common cancer in HIV-infected untreated individuals. Kaposi's sarcoma-associated herpesvirus (KSHV; also known as human herpesvirus 8 (HHV8)) is the infectious cause of this neoplasm. In this Review we describe the epidemiology of KS and KSHV, and the insights into the remarkable mechanisms through which KSHV can induce KS that have been gained in the past 16 years. KSHV latent transcripts, such as latency-associated nuclear antigen (LANA), viral cyclin, viral FLIP and viral-encoded microRNAs, drive cell proliferation and prevent apoptosis, whereas KSHV lytic proteins, such as viral G protein-coupled receptor, K1 and virally encoded cytokines (viral interleukin-6 and viral chemokines) further contribute to the unique angioproliferative and inflammatory KS lesions through a mechanism called paracrine neoplasia.

Introduction

The pathobiology of Kaposi's sarcoma (KS) retraces the history of modern viral oncology. From an oncological curiosity described more than 100 years ago to an AIDS-defining cancer, the discovery of Kaposi's sarcoma-associated herpesvirus (KSHV; also known as human herpesvirus 8 (HHV8)) and its oncogenic enigmas has enlightened many fields of tumour biology and viral oncogenesis. KS was first described as a skin cancer affecting elderly, mainly Jewish men of Ashkenazi origin in Vienna, Austria[1]. In 1981, physicians in New York, USA, and Los Angeles, USA, observed an epidemic of this disease affecting young, homosexual men[2, 3]. This KS epidemic was the first indicator of a devastating pandemic to follow, caused by the soon to be discovered HIV1 (Refs 4, 5). In 1994, a group at Columbia University, New York, USA, used representational difference analysis[6] (a PCR-based technique) to make a seminal discovery: DNA sequences of a new γ-herpesvirus were invariably present in KS lesions, but not in unaffected skin or most other diseased

tissues, thereby coining the term KSHV[7]. KSHV fulfils most of the modern-day Koch's postulates[8] causally linking this oncogenic virus with a human cancer. The full genome of KSHV has been sequenced[9] and studies on individual open reading frames (ORFs) have led to the discovery of new mechanisms for oncogenesis (such as the putative role of transiently expressed viral genes) and novel functions for cellular orthologues that are encoded by this virus. KS remains one of the most important and interesting viral-induced cancers that affects humans, and the discovery of KSHV[7] heralded a bourgeoning area for epidemiological, molecular and clinical research in viral oncology (Timeline). In the 15 years since its discovery, we have gone from not knowing what causes KS, to having a substantial understanding of the causative agent, its major virological and pathophysiological features, and potential rational targets for intervention.

But many key questions regarding this pathogen and its associated tumours remain unanswered. As a result of the AIDS pandemic, KS has become one of the commonest cancers affecting men and children in many subequatorial African countries, where it is associated with significant morbidity and mortality[10, 11]. Although the incidence of AIDS-associated KS (AIDS-KS) in the Western world has declined since the widespread implementation of highly active antiretroviral treatment (HAART), up to 50% of patients with AIDS-KS never achieve total remission[12]. Furthermore, although treatments for KS exist, none is curative. In this Review we discuss the current knowledge of KS oncogenesis and approaches towards rationally designed therapies and prevention that could affect the large AIDS-KS health burden.

Epidemiology of KS

KS is grouped into four epidemiological forms[13]: classic KS affecting elderly men of Mediterranean or eastern European Jewish ancestry; endemic KS, existing in parts of Central and Eastern Africa, described long before the HIV pandemic and often affecting children with disseminated lymphadenopathy[14, 15, 16]; iatrogenic KS, developing in immunosuppressed individuals after an organ transplant, for example[17]; and epidemic or AIDS-KS, a major AIDS-defining malignancy. In the Western world, AIDS-KS predominantly affects HIV-infected homosexual men. However, in Africa, since the spread of HIV, epidemic KS has become more common in both sexes, with a dramatic lowering of the male to female ratio, especially in East Africa[18].

KSHV-specific antibody titres correlate with viral load, and individuals with a low viral load consequently have lower antibody titres that might be missed by current serological assays. Therefore, there is the possibility of underestimating overall prevalence. However, despite this caveat and some regional exceptions, there is a strong concordance between KSHV seroprevalence rates and the incidence of KS (Fig. 1).

In Mediterranean populations, where classic KS exists, and in sub-Saharan Africa, where childhood KS occurs, mother-to-child transmission of KSHV through saliva is the most likely route of transmission[19, 20]. In HIV-infected homosexual men, where the risk for transmission is associated with the number of sexual partners, it is likely that the most probable route of transmission is also through saliva[21, 22]. These epidemiological

associations concur with the observation that KSHV can replicate *in vitro* in primary oral-derived epithelial cells[23]. Although KSHV transmission by blood transfusion or transplanted organs is documented, based on cost–benefit analyses most countries do not yet routinely screen blood or organ donors for KSHV infection.

Although KSHV infection is necessary for KS to develop, it is not sufficient and cofactors exist. The most important cofactor is HIV infection. KS incidence is 1 in 100,000 in the general population, but in HIV-infected individuals it is around 1 in 20 (Ref. 13), climbing to almost 1 in 3 in HIV-infected homosexual men before the introduction of HAART[24]. There has been extensive debate regarding whether immunodeficiency itself is the main determinant of KS, or whether HIV has a more direct role. Individuals with iatrogenic immunosuppression, particularly patients with renal transplants, also have an increased risk for KS, but this increase is not as great as that seen with HIV infection. This may reflect differences in KSHV infection rates, rather than HIV-specific causes, or differences in immune dysfunction, although a role for HIV as a cofactor has not been excluded. Individuals acquiring KSHV infection with pre-existing HIV infection have a significantly higher risk of developing KS; almost 50% develop KS, indicating that in this setting KSHV is one of the most oncogenic human viruses currently known[25]. This suggests that an already damaged immune system predisposes to a higher KSHV load, with subsequent KS development. Countries in which KS was endemic before the AIDS epidemic have seen a dramatic increase in the incidence of KS. Currently, KS is one of the most common cancers in certain sub-Saharan African countries[18, 26] where 89% of all KS cases occur, and only ~12% of patients are alive at 5 years after diagnosis[10].

The observation that in higher incidence groups and endemic areas, most HIV-negative KSHV-infected individuals never develop KS suggests that host factors have an important role. Studies have started to explore the potential contribution of host genetic factors, including genetic polymorphisms of inflammatory and immune-response genes. Classic KS risk is associated with diplotypes of interleukin-8 receptor-β (IL8RB), IL-13 (Ref. 27) and certain human leukocyte antigen (HLA) haplotypes[28, 29]. Transplant KS risk is associated with an *IL6* promoter polymorphism[30], and genotypes of FcγRIIIA influence the development of KS in HIV-infected men[31]. So far, these association studies have been small, and only show a slight overall increased risk.

These data suggest that common host genetic variants, in addition to environmental factors, timing and possibly routes of infection, all contribute to the oncogenic outcome of KSHV infection.

KS histogenesis

The histological features of the four epidemiological forms of KS are indistinguishable. They consist of spindle cells (the tumour cell), a proliferation of abnormal and leaky vessels and extravasated red blood cells with haemosiderin deposits[3, 32, 33]. A prominent inflammatory infiltrate is also present early in the development of these lesions (Fig. 2). Clinically, lesions have been described as patch, plaque, nodule and tumour stages, but as the same patient can have different types of lesions, and flat lesions (patch or plaque) can occupy extensive areas, and raised lesions (nodule or tumour) can be localized, the AIDS

Clinical Trials Group (ACTG) tumour staging classification is more often used as a measure of the extent of disease in clinical studies[34, 35]. AIDS-associated KS can present as an aggressive disseminated disease affecting skin, lymph nodes and visceral organs.

The cellular origin and neoplastic nature of KS remains contentious. The most common cell type in nodular lesions is the spindle-shaped cells (also known as KS cells). The vast majority of these spindle cells express endothelial markers, including CD31, CD34 and Factor VIII, but also markers of lymphatic endothelium, such as vascular endothelial growth factor receptor 3 (VEGFR3), lymphatic vessel endothelial hyaluronan 1 (LYVE1), D2-40 and podoplanin[36, 37] (Fig. 2). However, a few spindle cells also express markers of dendritic cells (Factor XIII), macrophages (CD68) or smooth muscle cells (SMA), leading to the idea that these cells do not represent a uniform cell type[38]. Ultrastructurally, spindle cells have features of both the lymphatic and vascular endothelium[39]. The observation that KSHV infection of blood vessel endothelial cells *in vitro* induces lymphatic endothelial markers, and infection of lymphatic cells leads to reprogramming towards blood vessel cells[40, 41], adds to the complexity. We suspect that KSHV infects circulating endothelial precursor cells, driving them towards a lymphatic lineage. Other oncogenic viruses such as Epstein–Barr virus (EBV) and human papilloma virus (HPV) are known to infect either B cell precursors or keratinocyte precursors, respectively, and exploit their differentiation for viral maturation and replication. Circulating vascular progenitors have certain KS spindle cell markers[36, 42], and infection of these cells would be consistent with the multifocal presentation of advanced KS[43, 44, 45] and the reported donor origin of post-transplant KS[46].

Reactive inflammation or true neoplasm?

The propensity of KS lesions to localize to scar tissue or sites of inflammation (known as the Koebner phenomenon)[47] provided one of the first clues that KS tumour cells are attracted by certain chemokines and flourish in a cytokine-rich microenvironment. In many early KS lesions the spindle cells are outnumbered by inflammatory cells. Therefore, before the discovery of KSHV, AIDS-KS research focused on the role of AIDS-associated cytokines and HIV-encoded proteins in driving inflammation and spindle cell proliferation (reviewed in Refs 48, 49). Various inflammatory cytokines increase in HIV pathogenesis[50], including IL-1, tumour necrosis factor-α and interferon-γ, promote KS spindle cell proliferation, induce spindle-like cell morphology in endothelial cells and spindle-like differentiation in circulating endothelial progenitor cells[43]. Explanted KS spindle cells differ from most other tumour cells as they are dependent on external cytokines and growth factors to grow *in vitro* and do not induce tumours in nude mice, unlike truly transformed cells. However, in the presence of inflammatory cytokines, cells isolated from KS lesions are able to induce KS-like lesions in immunodeficient mice[51]. Cytokines and growth factors with autocrine and paracrine growth effects in spindle cells include T helper 1 (T_H1) inflammatory cytokines, and cytokines and growth factors with pro-angiogenic activity such as IL-6, Oncostatin M[52], hepatocyte growth factor (also known as scatter factor)[53], fibroblast growth factor 2 and VEGF[54]. As discussed below, these cytokines are key mechanistic components in KS pathogenesis because their secretion is induced by KSHV infection, and they are necessary as autocrine and paracrine factors for driving KSHV oncogenesis.

Clinical observations are consistent with a deregulated inflammatory-driven angiogenic process, as KS seems to be more multifocal than metastatic, and regression of AIDS- and transplant-KS can occur when immune responses are partially restored during HAART or when immunosuppression is reduced. Adding controversy to the inflammatory versus neoplastic debate, X chromosome inactivation studies in single lesions as well as comparisons of multiple lesions from a single patient support a clonal origin in a subset of advanced cases only[55]. Most lesions are polyclonal, and multiple lesions from the same individual are also mainly polyclonal[56, 57]. The currently accepted interpretation of these data is that KS starts as a hyperplastic polyclonal lesion that is associated with inflammation and KSHV infection that could give rise, under specific circumstances like immunosuppression or other selective pressures, to clonal metastatic lesions. Supporting the idea that KS is only truly neoplastic in advanced stages is the observation that cellular oncogenic alterations, such as p53 and KRAS mutations or BCL-2 overexpression, as well as gene copy number changes, occur only in late-stage advanced disease[58, 59, 60]. Therefore, KS has features reminiscent of post-transplant lymphoproliferative disorders, which are EBV-driven B cell proliferations progressing from polyclonal hyperplasia to monoclonal tumours, and eventually to malignant lymphoma with oncogene and tumour suppressor alterations[61]. The proliferative nature of the spindle cells in the lesion, driven by latent viral proteins affecting cellular proliferation and survival (see below), concurs with many of the existing paradigms of cancer. However, the heterogeneous, multiclonal cellular composition of KS, the involution of KS following an immune response, the probably important role of infiltrating inflammatory cells, and the key role that the release of inflammatory and angiogenic mediators by KSHV-infected cells has in driving KS tumorigenesis (see below), exemplify an inflammatory-driven oncogenic process or paracrine neoplasia[62].

Mechanisms of KSHV-induced oncogenesis

KSHV infection of endothelial cells or circulating endothelial and/or haematopoietic progenitors[45, 63] leads to changes in their morphology[64], glucose metabolism[65] growth rate, lifespan and gene expression[40, 41, 66, 67], resulting in the precipitation of KS. KSHV oncogenicity is reflected by the numerous pro-angiogenic molecules that are induced after infection of endothelial cells, including members of the VEGF–VEGFR family, angiopoietin family, cyclooxygenase 2 (COX2) and angiogenin[41, 68, 69, 70, 71]. However, in most experimental systems, *in vitro* infection of endothelial cells with KSHV leads to morphological changes and an extended lifespan and provides a survival advantage in response to apoptotic stimuli, but not full neoplastic transformation. Moreover, although KSHV encodes oncogenic genes that could potentially induce all KS-related malignant phenotypes (see below), KSHV infection in the general population rarely leads to KS. This underscores the existence of cofactors, such as HIV or drug-induced immunosuppression, that are required for the virus to induce a tumour.

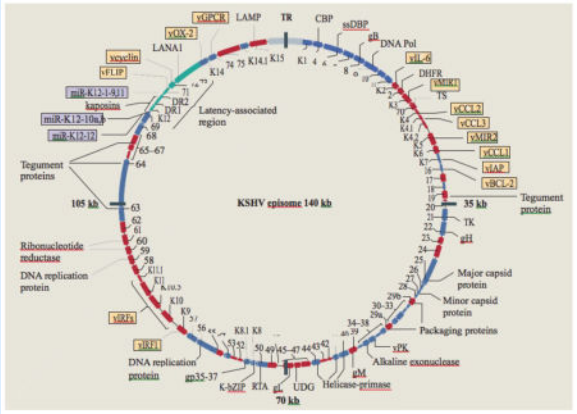
Although the vast majority of KS spindle cells are latently infected with the virus[37, 72] (Box 1), in a small proportion of infected cells the virus undergoes lytic replication leading to the production of mature virus and cell lysis. Apart from the viral cyclin (vcyclin) and viral FLICE inhibitory protein (vFLIP), the other cellular orthologues that are encoded by KSHV are early lytic genes that are generally expressed only in cells in which the virus is

undergoing lytic replication. However, certain KSHV immunoregulatory and growth-promoting genes, including vIL-6, vMIR3 and vMIR5, could be activated by Notch signalling independently of the lytic transactivator RTA[73]. Moreover, limiting-dilution reverse transcription-PCR analysis shows that transcripts such as vIL-6 can be expressed in KSHV latency in a context-dependent manner; for example, in B cell lines[74]. This implies that the expression of KSHV genes might not be restricted by the classic herpesviral paradigm of latent or lytic infection, as lytic genes can be expressed without the full execution of the lytic cycle[75]. This is an important observation when we consider the complementary role of latent and lytic gene-expressing cells in KS pathogenesis.

Box 1

The KSHV episome

Kaposi's sarcoma-associated herpesvirus (KSHV; also known as human herpesvirus 8 (HHV8)) has at least four major subtypes that track human migration through Africa (predominantly subtype B and A5); the mediterranean (subtype C); northern Europe and North and South America (A); and the Far East (D)162. KSHV encodes 87 open reading frames (ORFs) and at least 17 microRNAs (purple boxes), 14 of which are co-expressed as a cluster. A striking feature of KSHV is the number (at least 14) of ORFs that encode cellular orthologues. Identified ORFs and encoded proteins are indicated in the figure. Putative latent transcripts are indicated in green, and cellular orthologues in yellow. Infection occurs when mature virions anchor to specific cellular receptors. After viral glycoprotein binding to the necessary receptors, clathrin-mediated endocytosis facilitates entry into cells163. Following infection, rapid circularization of the viral genome occurs164 and, like other herpesviruses, KSHV exists as an episome (double-stranded circular DNA) within the host nucleus. Reactivation can occur when the promoter of ORF50 is activated (by demethylation, for example)165, resulting in the expression of replication and transcription activator (RTA), the main regulator for the viral lytic replication programme77, 166. Early lytic genes include those encoding viral proteins required for DNA replication or viral gene expression, whereas late lytic genes are those encoding viral structural proteins, such as envelope and capsid proteins, that are required for assembly of viral particles (virions).



Primary effusion lymphoma (PEL) cells are latently infected with KSHV[76] and were instrumental in classifying KSHV genes as latent or lytic, and identifying the major effectors of latent and lytic replication[77, 78]. Many observations made from PEL-derived tumours, such as the switch to lytic replication that occurs during *in vivo* growth[79], are also observed in KS models, indicating that PEL is a valid model to study aspects of KSHV biology. Simple *in vitro* models, such as NIH3T3 and 293 cells, together with more sophisticated single gene transgenic mice have been instrumental in gaining molecular and functional information on individual viral genes. The potential contributions of individual latent and lytic viral infection to KS oncogenesis, together with emerging theories on how they collaborate (Fig. 3) are summarized below. The mechanisms by which KSHV perturbs normal immune responses and evades host immunity, are reviewed elsewhere[80, 81].

Latent KSHV infection

The major latency viral transcripts expressed in KS spindle cells are from the same genomic region and include the expression of the latency-associated nuclear antigen (LANA), vcyclin, vFLIP, viral-encoded microRNAs (miRNAs), as well as kaposins (Box 1). These transcripts endow growth and proliferative signals, evasion of apoptosis, pro-angiogenic and inflammatory signals, as well as limitless replicative potential. However, together these viral transcripts have not been shown to transform endothelial or any other cells *in vitro*. Although the main function of LANA is to maintain the viral episome[78], LANA can also interfere with important anti-tumorigenic pathways (Fig. 3): LANA inhibits the activities of the p53 (Refs 82, 83) and the RB–E2F tumour suppressor pathways[84]. In addition, LANA has been shown to deregulate Wnt signalling by nuclear trapping of glycogen synthase kinase 3β (GSK3β), thereby stabilizing β-catenin[85], and to inhibit anti-proliferative transforming growth factor-β (TGFβ) signalling by epigenetic suppression of TGFβ receptors[86]. LANA might contribute to angiogenesis, by stabilizing hypoxia-inducible factor 1α (HIF1α) and by targeting von Hippel Lindau (VHL) for degradation[87]. LANA is also an activator of telomerase reverse transcriptase (TERT) expression[88] and can increase the lifespan of human umbilical vascular endothelial cells (HUVECs)[89].

vcyclin[90] is a constitutive activator of cyclin-dependent kinase 6 (CDK6)[91] and, strikingly, has activities that are not restricted to cellular D-type cyclins[92, 93]. vcyclin expression leads to cytokinesis defects and polyploidy, which activates p53. However, in the absence of functional p53, such cells survive, exposing the oncogenic potential of vcyclin[94]. The exact function of this viral protein, in the context of all other viral proteins, is still not clear, but it is likely that vcyclin drives cellular proliferation and so promotes viral replication. It has been suggested that genomic instability is an inevitable consequence of latent KSHV infection, owing to vcyclin–CDK6-mediated phosphorylation of nucleophosmin (NPM1)[95, 96].

vFLIP binds to inhibitor of κB kinase-γ (IKKγ), leading to the direct activation of nuclear factor-κB (NF-κB)[97, 98] (Fig. 3). A large number of cytokines, including chemokines implicated in KS pathogenesis, are induced in endothelial cells by vFLIP activation of NF-κB[99, 100]. In addition to cytokine secretion, constitutive NF-κB activation by vFLIP could have important anti-apoptotic roles in oncogenesis by leading to the induction of proteins

that inhibit apoptosis, such as BCL-2 and BCL-X_L[101]. Interestingly, vFLIP also suppresses autophagy, an important pro-oncogenic activity, by preventing ATG3 from binding and processing LC3 (Ref. 102). vFLIP is also responsible for the spindle cell morphological transformation of endothelial cells *in vitro*[103].

Kaposins are proteins that are encoded by the alternatively spliced ORF K12 (Ref. 104). Kaposin A is a latent protein with transforming potential in rodent fibroblasts[105]. Kaposin B affects signalling by binding to MK2, a MAPK-associated protein kinase. Kaposin B-mediated activation of MK2 blocks the decay of mRNAs with AU-rich elements (AREs) in their 3′ untranslated regions. As several cytokine mRNAs have ARE elements, kaposin B expression results in an increase in the production of pro-inflammatory cytokines[106]. Therefore, vFLIP, kaposin A and kaposin B are likely to contribute to the inflammatory microenvironment of KS.

Mice that express a LANA transgene using the natural viral promoter, a vFLIP transgene (using an H2κB promoter and IgH enhancer), or vcyclin transgene using the Eμ promoter and enhancer, develop lymphoid malignancies with low frequency and after a long latency[108, 109, 110]. Although these findings support the idea that LANA, vcyclin and vFLIP could drive B cell proliferation and survival, the induced tumours fail to exhibit characteristics of KSHV lymphoproliferations, such as a plasmablastic phenotype.

Certain transgenic models develop lesions with KS characteristics. For example, mice expressing vcyclin targeted to lymphatic endothelium using a *Vegfr3* promoter develop lymphatic abnormalities and oedema[111]. Concurring with *in vitro* data, there is no obvious proliferation or transformation of lymphatic endothelial cells *in vivo*, only their aberrant development and leakiness. Although transgenic animals that express individual viral ORFs provide useful information about the *in vivo* functions of a specific viral protein, these viral ORFs are expressed out of the context of global viral replication and persistence, and so data must be interpreted with caution.

The KSHV-encoded miRNAs are expressed in latently infected cells[112, 113, 114] and are thought to be involved in suppressing the lytic reactivation of the virus, and are thought to influence endothelial cell differentiation and angiogenesis. One viral miRNA, miR-K1, targets IκBα, an inhibitor of NF-κB. NF-κB inhibits the activation of lytic viral promoters[115]; therefore, by activating NF-κB, this miRNA suppresses viral lytic replication, maintaining latent infection[116]. The viral miRNAs also inhibit the anti-angiogenic molecule thrombospondin 1 (Ref. 117), possibly contributing to KS-related angiogenesis. At least four of the viral miRNAs, including the orthologue of cellular miR-155, target the cellular oncogene MAF to induce reprogramming of lymphatic endothelial cells[118]. By studying the viral miRNAs, MAF was identified as a potential transcriptional repressor that functions in endothelial cells. These viral miRNAs could thus influence the differentiation of infected endothelial cells, contributing to KS development. KSHV also induces cellular miRNAs. One of the most upregulated miRNAs after the infection of endothelial cells and in KS lesions, is miR-132 (Ref. 119). This miRNA not only inhibits anti-viral innate immune responses[119], but intriguingly also induces abnormal endothelial cell proliferation[120].

Therefore, this miR-132 could link two important features of KS: viral immune escape and angiogenesis.

Lytic KSHV infection

Many lytic viral proteins such as K1, the viral interferon response factors (vIRFs), vIL-6, the viral-encoded chemokines (vCCLs), viral G protein-coupled receptor (vGPCR) and K15, which are expressed by a proportion of cells in KS lesions, have impressive putative tumorigenic activities and so could contribute to the angiogenic and inflammatory phenotype of KS lesions. By activating RAC1 and RHOA, vGPCR induces the activation of MAPKs, AKT and NF-κB, resulting in cell proliferation[121, 122], secretion of VEGF[122, 123] and other pro-angiogenic and inflammatory cytokines such as angiopoietin 2 (ANGPT2)[124], IL-6 and IL-8 (Refs 125, 126).

Mice expressing transgenic vGCPR develop angiogenic lesions that resemble KS[127, 128], as vGPCR is only expressed in a proportion of cells, and these cells drive VEGF-mediated angiogenesis using paracrine mechanisms[62]. As vGPCR is not expressed during latency and therefore not by most tumour cells, paracrine models more accurately reflect its role in KS biology[129].

A transgenic model of endothelial cell-specific transduction using an avian retrovirus and testing several KSHV lytic and latent genes, showed that vGPCR is the only ORF that has the ability to initiate angiogenic lesions[130]. This system identified RAC1 as a mediator of vGCPR oncogenesis[131] and added to the evidence that vGCPR activates TSC2–mTOR signalling, making mTOR a potential therapeutic target in KS[132]. RAC1 is involved in the production of reactive oxygen species (ROS) through NADPH oxidases and is overexpressed in all KSHV-infected cells in KS lesions. Moreover, constitutive activation of RAC1 induces angiogenic lesions in mice[133]. Overall, vGPCR could promote infected endothelial cell proliferation, angiogenesis and the recruitment of an inflammatory infiltrate through autocrine and paracrine mechanisms (Box 2; Fig. 3).

Box 2

Animal models for virally induced KS

Animal models of γherpesvirus infection and pathogenesis include the mouse herpesvirus 68 (MHV68)167 and the Rhesus rhadinovirus (RRV)168 models. Although these viruses are related to Kaposi's sarcoma-associated herpesvirus (KSHV; also known as human herpesvirus 8 (HHV8)), they generate B cell lymphoproliferation, and are of limited use to study Kaposi's sarcoma (KS) pathogenesis. The squirrel monkey γherpesvirus, herpesvirus saimirii, induces lymphomas when infecting non-natural hosts such as owl monkeys, but never endothelial tumours. The retroperitoneal fibromatosis herpesvirus (RFHV) induces retroperitoneal fibrosis (RF) in animals that become immunodeficient after infection with a simian virus. The spindle-shaped cells in these RF lesions express the latency-associated nuclear antigen (LANA) orthologue of RFHV169, but these spindle cells belong to the mesenchymal rather than the endothelial lineage. These lesions are not relevant to KS biology.

Two cell lines bearing the KSHV genome generate KSHV-infected tumours. One is based on HUVECs that express telomerase (TIVE-LTC)170 and the other is based on an infectious bacterial artificial chromosome (KSHVBac36) transfected into normal mouse bone marrow endothelial lineage cells (mECK36)171 (Fig. 4). Both systems suggest that KSHV tumour formation requires both latent and lytic viral gene expression. This observation contrasts with mechanisms underlying classic viral-induced tumours, such as Epstein–Barr virus-driven lymphoma or human papilloma virus-associated cervical cancer, in which latent viral proteins (including viral oncogenes) are expressed in clonally derived cells, and lytic or abortive infection plays little, if any, role. The mECK36 system has viral and host transcriptome characteristics that are related to those found in KS. This model demonstrates the *de novo* tumorigenicity of KSHV infection in normal mouse cells, showing that KSHV provides a survival advantage to cells *in vivo*, and a role for viral G protein-coupled receptor in vascular endothelial growth factor-mediated angiogenesis in the context of KSHV-induced tumours. Some studies have used different types of humanized immunodeficient mice to establish a more physiologically relevant *in vivo* model of KSHV infection of human cells, but these models fail to generate KS-like tumours172, 173. Common marmosets are susceptible to KSHV infection, and one of the infected animals developed a KS-like tumour, expressing both latent and lytic viral proteins174.

Other notable lytic viral proteins that could have a role in KS pathogenesis include the cellular orthologues vIL-6, vBCL-2, vIRFs and vCCLs. The gp130-binding IL-6R modulated vIL-6 virokine[134] is angiogenic[135] and might induce spindle cell proliferation and survival. The vCCLs are angiogenic in various experimental systems, promoting endothelial cell proliferation and migration, and could also curtail the local immune response against virally infected cells[136, 137]. vBCL-2 (Ref. 138) inhibits apoptosis[139] through the inhibition of pro-apoptotic BH3 domain-containing proteins[140]. Several vIRFs inhibit p53-induced apoptosis[141]. In particular, vIRF1 inhibits DNA damage-induced apoptosis by inhibiting ATM activation of p53, a mechanism that could lead to resistance to genotoxic drugs and the accumulation of mutations and genetic instability[142]. vIRF3 activates VEGF secretion by stabilizing HIF1α[143].

The first ORF of KSHV, K1, has substantial diversity between viral isolates, and is used to sub-classify KSHV into A, B, C and D strains (Box 1). All K1 subtypes seem to function similarly. K1 activates the PI3K–AKT anti-apoptotic pathway, inducing survival factors such as VEGF that can function in an autocrine and paracrine manner[144]. K1 can also suppress CD95-mediated apoptosis[145]. The main role of lytic viral proteins inhibiting apoptosis (like vBCL-2, vIRF1 and K1) could be to delay apoptosis during lytic replication, thus providing time for virion production and assembly, before cell lysis. Like K1, the SH2 and SH3 domain-containing K15 also flanks the terminal repeat region of the KSHV episome (Box 1), activates the NF-κB and MAPK pathways and induces the expression of several inflammatory and angiogenic genes[146, 147].

Interplay between latent and lytic KSHV-infected cells in KS paracrine oncogenesis

Both latent and lytic KSHV genes contribute to the malignant phenotype of KS. However, lytic infection is unlikely to have any direct role in endothelial cell autonomous growth, transformation or immortalization, as lytic viral gene expression is generally associated with viral replication and cellular lysis. During lytic infection, KSHV ORF 37, a homologue of a DNA exonuclease, is also responsible for wide-scale cellular mRNA degradation, inhibiting host gene expression and therefore curtailing the role of cellular proteins during oncogenesis[148]. One theory currently gaining experimental support is that in order for latent genes to drive oncogenic cell proliferation, they need to be enhanced, in a paracrine manner, by host and viral growth factors and cytokines supplied by a minority of lytically infected cells and/or lytic gene-expressing cells that are present in KS lesions[62, 122] (Fig. 3). Paracrine-acting factors such as VEGF, ANGPT2, platelet-derived growth factor (PDGF), GROa and IL-6 induced by lytic genes such as vGPCR, K1 and K15, in addition to vIL-6 and the vCCLs, could be necessary to drive latently infected cell proliferation, induce angiogenesis and inflammation, and further support the recruitment of uninfected cells, as well as the survival and immune escape of latently infected cells that form the majority of the KS tumour. The role of lytic infection in KS pathogenesis is supported by several observations. First, lytic viral proteins are expressed and virions are present in a minority of cells within KS lesions[72, 149]. Second, immunosuppression increases KSHV re-activation and lytic replication. Third, interrupting lytic replication by immune reconstitution or by anti-lytic herpes anti-virals, such as gancyclovir, can also inhibit or prevent KS development[150, 151, 152]. Fourth, lytic infection seems to be necessary to support viral episomal maintenance by the recruitment of new cells to latency to replace those that have segregated their viral episome[153]. Last, co-injection of vGPCR-expressing cells is necessary to induce tumour formation by cells expressing only latent genes[154]. The proposed molecular interplay between latent and lytic genes resulting in KS is shown in Fig. 3.

Rational treatment

Underscoring its dependence on HIV infection and immunosuppression, HAART has reduced the incidence of AIDS-KS, and can induce AIDS-KS regression. Mechanisms are likely to include immune reconstitution against KSHV[152] and possibly decreasing circulating HIV-associated pro-angiogenic and inflammatory cytokines[13]. In addition, HIV protease inhibitors have direct antitumour activity[155], although non-protease-containing HAART combinations also induce KS regression[156]. Despite the widespread availability of HAART in the Western world, KS remains a clinical problem with only around 50% of patients achieving complete resolution[12]. In addition to HAART, radiotherapy for isolated lesions and systemic chemotherapy, including liposomal daunorubicin and taxanes, are useful for disseminated disease. Our understanding of the molecular basis and biology of KS is leading to rational therapeutic trials and drug design[157, 158](Table 1). Promising approaches aim to intervene in the paracrine and autocrine mechanisms depicted in Fig. 3 and include targeting the angiogenic or lymphangiogenic axis of VEGFA–VEGFR2, VEGFC–VEGFR3, as well as ANGPT2 and the proliferative and vascular growth factor PDGFβ (Fig. 4). Another angiogenesis-related target in KSHV oncogenesis is the Notch pathway[159], which could potentially be targeted by γ-secretase inhibitors and inhibitors of

Notch ligand interactions, including delta-like ligand 4 (DLL4)[160, 161]. Targeting the IKKγ–vFLIP interaction with specific small molecules should provide specific inhibition of KSHV-induced NF-κB without interfering with normal cellular NF-κB pathways. Targeting mTORC1 using rapamycin was serendipitously found to be effective in post-transplant KS and is currently being used to prevent and treat this disease. Although the exact mechanism for KS inhibition by rapamycin is still unclear, it is thought that rapamycin interferes with the dependence of KS cells on the PI3K–AKT–mTORC1 pathway, which is activated by several KSHV genes and is essential for promoting cytokine and angiogenic growth secretion that is central to KSHV-induced oncogenesis.

Future perspectives

KS is an unusual tumour with features pertinent to viral oncogenesis, inflammation and cancer. The large number of cellular orthologues encoded by this virus, and its ability to subvert multiple signalling pathways have attracted considerable research interest, which has been enhanced by new disease paradigms. Sixteen years after the discovery of KSHV as the causal agent of KS, and after more than 2,000 publications on this virus, KS remains a common and devastating disease in some geographic regions. Although palliative treatments exist, and the control of HIV infection is helpful in preventing KS or inducing its regression, there are no vaccines or curative drugs. Promising results in the laboratory and their successful translation to the clinic show that our improved understanding of KSHV pathobiology is leading to the development of better preventive and therapeutic approaches for KS.

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"At a glance" summary

- Kaposi's sarcoma herpesvirus (KSHV; also known as human herpesvirus 8 (HHV8)) is the causative agent of Kaposi's sarcoma (KS) and certain lymphoproliferations, and its seroepidemiology correlates with the global incidence of KS.
- KS is the most common neoplasm in untreated HIV-infected individuals, and also occurs in other states of immunosuppression, including after an organ transplant.
- KSHV is transmitted through saliva and replicates in oropharyngeal cells.
- Unlike most cancer cells, KS tumour cells are not fully transformed, do not show autonomous growth, and remain dependent on exogenous cytokines for *in vitro* growth.
- KS starts as a proliferation of endothelial-type cells, with an early onset inflammatory and abnormal leaky blood vessel expansion.
- KSHV is present in the vast majority of KS tumour cells (that is, spindle cells), expressing the latent viral proteins, including viral cyclin, viral FLICE inhibitory protein, latency-associated nuclear antigen (LANA) and a group of viral microRNAs.
- A proportion of cells in KS lesions seem to undergo lytic replication, expressing lytic viral proteins including K1, viral interleukin-6, viral BCL-2, viral G protein-coupled receptor, K15 and viral chemokines.
- KSHV latent genes drive cell proliferation and prevent apoptosis; whereas KSHV lytic genes could further contribute to KS tumorigenesis by triggering host signalling cascades that lead to cytokine and growth factor secretion.
- Biological insights into KSHV oncogenesis are leading to promising rational therapeutic approaches.

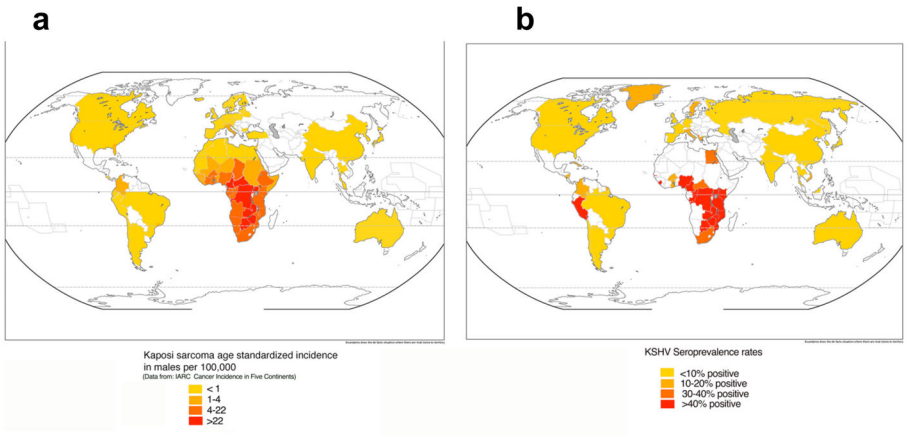


FIGURE 1. Geographical prevalence of KS and seroprevalence of KSHV

The standardized incidence of Kaposi's sarcoma (KS) is depicted for males, and was obtained from the International Agency for Research on Cancer Cancer Incidence in Five Continents publication (see Further information). The rate provided for the United States is an average, but rates in some States (including, California, New York, Georgia and the District of Columbia) can be as high as 6 in some subpopulations. According to Surveillance Epidemiology and End Results (SEER; see Further information) overall rates in the United States among non-Hispanic caucasians is 0.8, among caucasian Hispanics 1.4, and among African Americans is 2.4. In Italy, rates also vary by region, being as low as 0.2 in Umbria but 2.2 in Brescia. Incidences in Africa are taken from the Globocan database (see Further information). b | Seroprevalence rates were compiled from multiple studies. When different rates from the same country are reported, an average was taken. Values represent those in the general population, usually blood donors, and cohorts comprising of HIV-infected individuals were excluded. The seroprevalence of KSHV infection in northern Europe, Asia and the United States is less than 10%, but in most of sub-Saharan Africa, overall seroprevalence is more than 50%. The Mediterranean region has intermediate seroprevalence rates of 10–30%175.

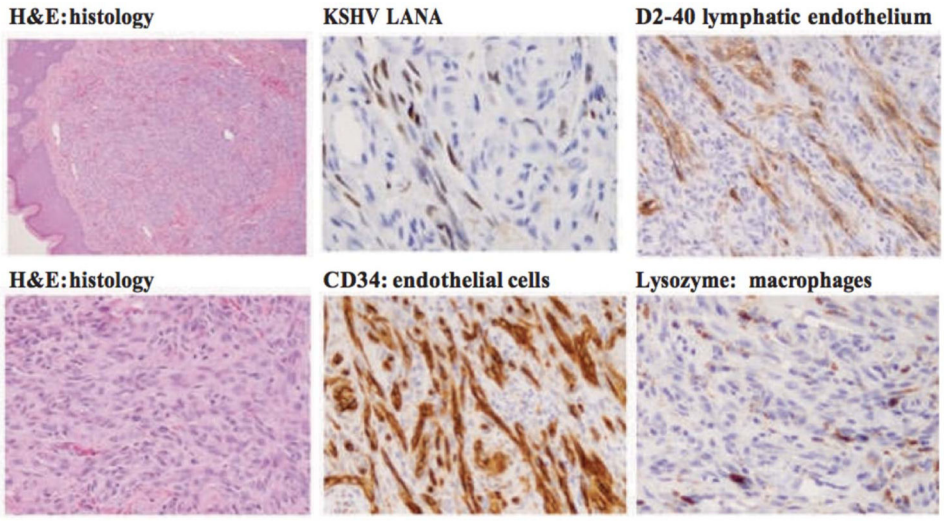


Figure 2. Cellular Heterogeneity in Kaposi's sarcoma

A biopsy sample from a nodular KS lesion showing numerous spindle cells in the dermis. Immunohistochemical staining shows Kaposi's sarcoma-associated herpesvirus (KSHV; also known as human herpesvirus 8 (HHV8)) latency-associated nuclear antigen (LANA) in spindle cells lining vascular spaces. The lymphatic marker D2-40 is also localized to vascular spaces. Kaposi's sarcoma (KS) lesions are composed of various cell types, including vascular (CD34) and lymphatic endothelial cells (D2-40), macrophages (lysozyme), lymphocytes, plasma cells and red blood cells. The inflammatory infiltrate is both inside and outside well-formed or poorly defined vascular spaces. These images highlight the complexity of KS lesions and the presence of virus in only a variable proportion of cells in the lesions, which is consistent with an important role of paracrine angiogenic and inflammatory signals. Magnifications: for hematoxylin and eosin (H&E) x10 and x40; for LANA x40; for CD34, D2-40 and lysozyme x20.

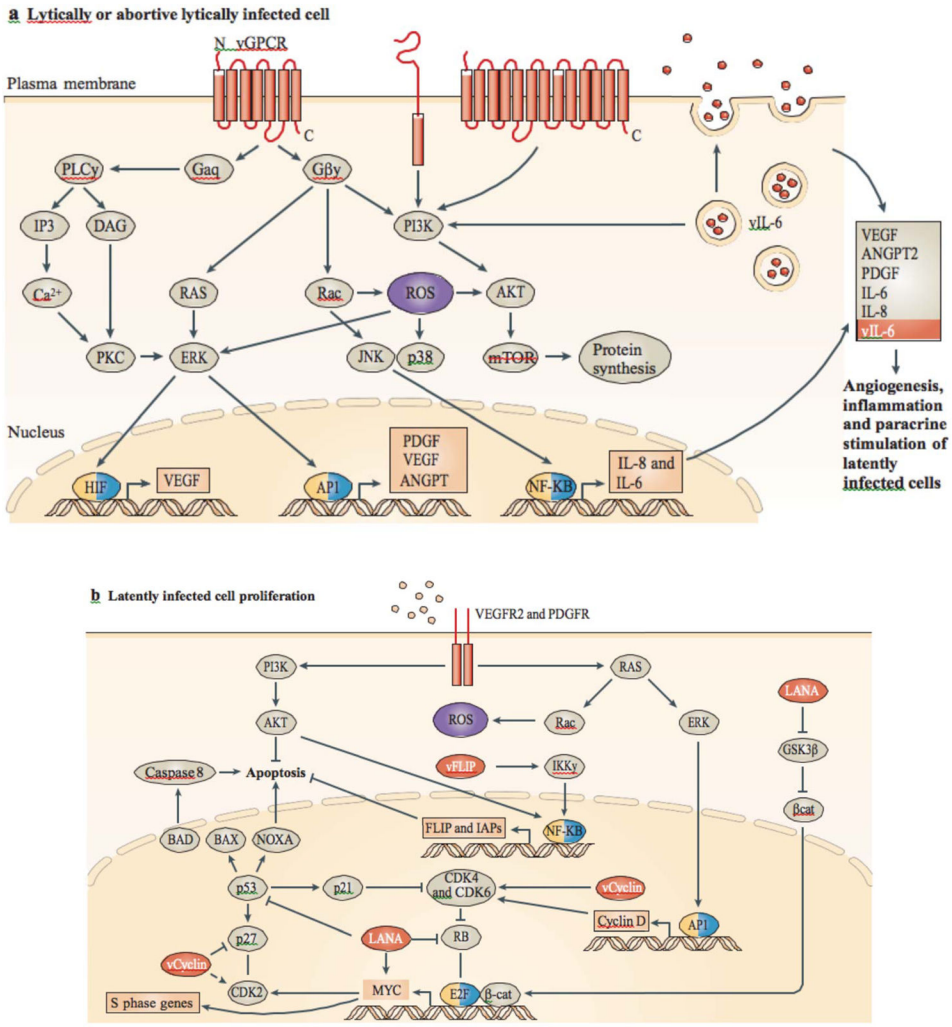


FIGURE 3. Proposed mechanism of KSHV-induced sarcoma

a | In lytic or abortive lytic-infected cells, expression of Kaposi's sarcoma-associated herpesvirus (KSHV; also known as human herpesvirus 8 (HHV8)) early lytic genes (such as viral G protein-coupled receptor (vGPCR), K1, viral interleukin-6 (vIL-6) and K15; shown in red) subvert host signalling pathways, leading to the expression and secretion of angiogenic, inflammatory and proliferative factors (including, vascular endothelial growth factor (VEGF), platelet-derived growth factor-β (PDGFB), angiopoietin 2 (ANGPT2), IL-6 and IL-8). This can occur together with intracrine activity and the secretion of vIL-6. **b** | Secreted factors stimulate their receptors in latently infected cells through a paracrine mechanism, complementing the autocrine (such as the secretion of cytokines by viral FLICE inhibitory protein (vFLIP)) and direct pro-oncogenic activities of KSHV latent genes, such as vFLIP, vcyclin and latency-associated nuclear antigen (LANA), as well as the KSHV-encoded microRNAs. β-cat, β-catenin; CDK, cyclin-dependent kinase; GSK3β, glycogen synthase kinase 3β; HIF, hypoxia-inducible factor; IAPs, inhibitor of apoptosis proteins; NF-κB, nuclear factor-κB; PKC, protein kinase C; PLC, phospholipase C; ROS, reactive oxygen species.

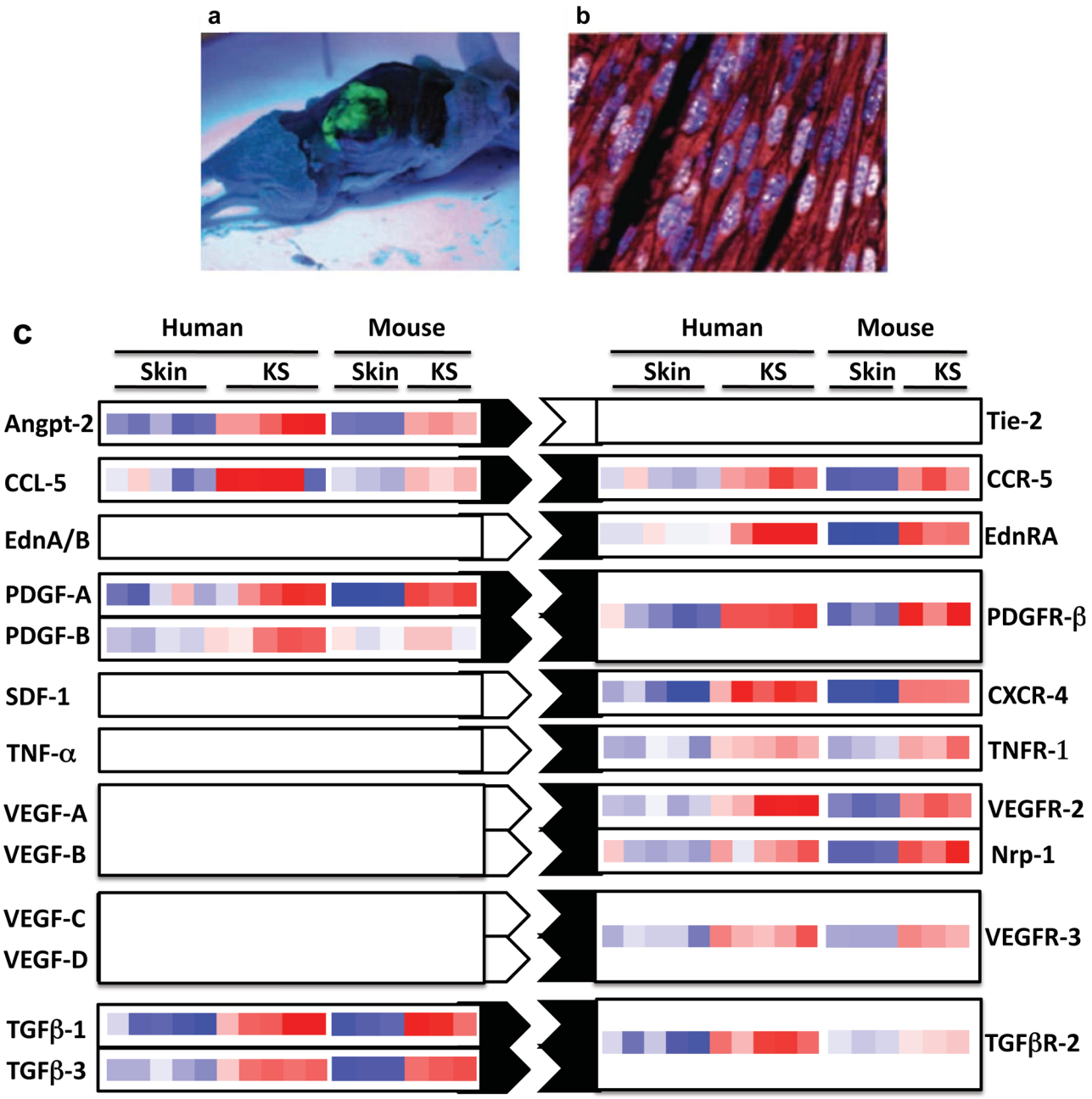
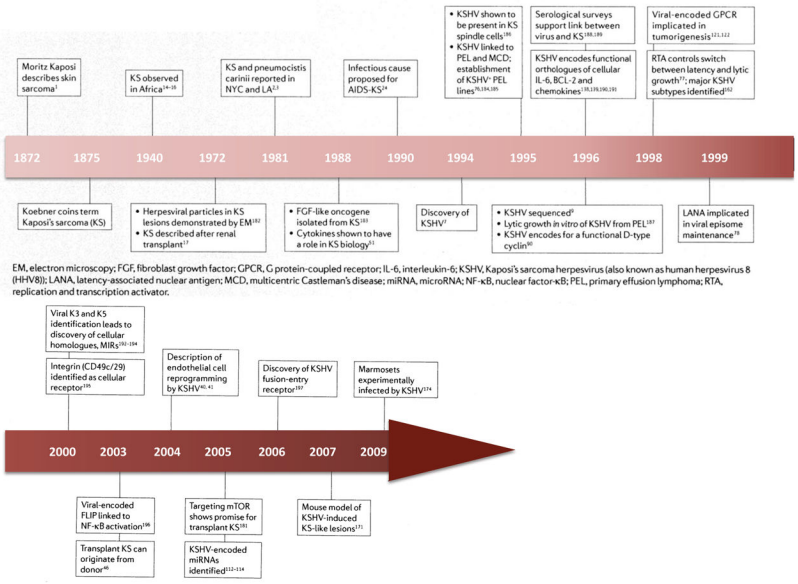


FIGURE 4. Mouse model of KSHV-induced KS

a | Nude mice bearing enhanced green fluorescent protein-expressing tumours that are induced by subcutaneous injection of mouse endothelial cells transfected with Karposi's sarcoma-associated herpesvirus (KSHV; also known as human herpesvirus 8 (HHV8)) KSHV Bac 36 (mECK36). **b** | Immunoflurorescence analysis of latency-associated nuclear antigen (LANA; white) and the Kaposi's sarcoma (KS) marker podoplanin (red) in mECK36 tumours showing punctuated LANA staining that is characteristic of episomal KSHV in cell nucleus (DAPI Blue). **c** | Activation of paracrine and autocrine endothelial stimulation as shown by gene expression data (heat maps) from AIDS-KS41 and from the

mECK36 mouse KS model171. Data are grouped by ligands (left) and receptors (right), which are present in both molecular signatures. Open connectors indicate paracrine stimulation by upregulation in KS of at least one of the receptor–ligand pairs; ligand and receptor closed connectors indicate upregulation of both receptor and ligand with potential for both paracine and autocrine stimulation. ANGPT2, angiopoietin 2; CCL5, chemokine, CC motif, ligand 5; CCR5, chemokine, CC motif receptor 5; CXCL12, chemokine CXC motif, ligand 12; EdnA, Endothelin A; NRP, neuropilin; PDGF, platelet-derived growth factor; TGFβ, transforming growth factor-β; TNF, tumour necrosis factor; VEGF, vascular endothelial growth factor.



Timeline.
A history of KS KSHV

TABLE 1

Potential new drugs for the treatment of KS

Target	Biological effect	Agent	Proposed mechanism of action	Current status	Refs
VEGFC, VEGFD and VEGFR3 axis	Inhibits lymphangiogenesis	Cediranib (AZD2171)	Tyrosine kinase inhibitor blocking VEGFR3	Phase II/III studies for various cancers, no clinical trials yet for KS	176
VEGFA	Inhibits angiogenesis	Bevacizumab, sorafenib, sunitinib and PTC299	Monoclonal antibody bevacizumab that targets VEGF and small molecules that inhibit VEGFR (as well as KIT and PDGFR). PTC299 inhibits the production of VEGF by targeting post-transcriptional VEGF synthesis	NCI Phase II bevacizumab with liposomal doxorubicin; NCI Phase and PTC299 is in preclinical development	177
ANGPT2	Inhibits angiogenesis and lymphangiogenesis		Blocks proliferation of KSHV-infected spindle cells that express ANGPT2	Inhibitors in preclinical development	41, 124, 178
DLL4	Vascular disrupting		In preclinical studies, blocking of DLL4-NOTCH signalling results in a paradoxical increase in tumour vessel density, but causes marked growth inhibition owing to functionally defective vasculature	Inhibitors in preclinical development	159, 160
NF-KB: vFLIP-IKKG	Inhibits inflammation, angiogenesis and cell proliferation		Small molecules currently being screened that could interfere with vFLIP-IKKG interaction	Preclinical development	97, 98
KIT and PDGFR	Inhibits spindle cell proliferation	Imatinib	KIT and PDGFR implicated in KS cell proliferation	Phase I	179, 180
mTOR	Modulates immunity and inhibits cell proliferation	Sirolimus, tacrilimus and evirulumus	Small molecules that inhibit mTOR. KSHV infection activates mTOR signalling, which is important for cell survival and angiogenesis	Phase II/III studies	132, 181

ANGPT2, angiopoietin 2; DLL4, delta-like ligand 4; IKKγ, inhibitor of κB kinase-γ; KSHV, Kaposi's sarcoma herpesvirus; KS, Kaposi's sarcoma; NCI, National Cancer Institutes; NF-κB, nuclear factor-κB; PDGFR, platelet-derived growth factor receptor; ROS, reactive oxygen species; VEGF, vascular endothelial growth factor; VEGFR, VEGF receptor; vFLIP, viral FLICE inhibitory protein.