Targeted therapy for Kaposi's sarcoma and Kaposi's sarcoma-associated herpesvirus

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Purpose of review

To summarize major recent findings on the biology of human herpesvirus-8, i.e. Kaposi's sarcoma-associated herpesvirus, and the implications of these findings for Kaposi's sarcoma treatment.

Recent findings

Although reduced in incidence in developed countries since the introduction of highly active antiretroviral therapy, Kaposi's sarcoma incidence is still markedly increased in HIV-infected patients in resource-rich areas of the world and is a major complication among HIV-infected individuals in sub-Saharan Africa. The Akt/mammalian target of rapamycin pathway has emerged as a major driving force in Kaposi's sarcoma. In addition, the roles of p53, the Kaposi's sarcoma-associated herpesvirus viral cyclin and nuclear factor-κB in the development and progression of Kaposi's sarcoma are being further clarified, and therapeutic agents are being developed that may target these pathogenetic mechanisms. New Kaposi's sarcoma treatments should be considered that target the molecular interface between virus and host.

Summary

The growing knowledge of Kaposi's sarcoma biology provides multiple opportunities for rational targeted therapies. Further research is needed to better understand the mechanisms by which Kaposi's sarcoma develops and to develop therapeutic strategies that prevent resistance to treatment.

Keywords

Akt/mammalian target of rapamycin, angiogenesis, Kaposi's sarcoma, Kaposi's sarcoma herpesvirus, viral cyclin

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Abbreviations

AMC	AIDS Malignancy Consortium
Cdk	cyclin-dependent kinase
HAART	highly active antiretroviral therapy
HHV	human herpesvirus
IFN	interferon
KSHV	Kaposi's sarcoma herpesvirus
MMP	matrix metalloproteinase
mTOR	mammalian target of rapamycin
NF	nuclear factor
PEL	primary effusion lymphoma
vCyc	viral cyclin
VEGF	vascular endothelial growth factor
vGPCR	viral G-protein-coupled receptor

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Introduction

Kaposi's sarcoma shows a gene expression profile resembling that of lymphatic endothelium [1,2] and requires infection with human herpesvirus (HHV)-8, also known as the Kaposi's sarcoma-associated herpesvirus (KSHV), for its development. Kaposi's sarcoma was among the first opportunistic diseases reported in association with HIV infection in the early 1980s and was one of the original conditions considered diagnostic of AIDS. Although the incidence of the tumor has declined markedly in developed countries since the introduction of highly active antiretroviral therapy (HAART), the standardized incidence ratio for Kaposi's sarcoma among people with AIDS remained more than 3600-fold higher in the post-HAART period (1996–2002) than in the general population in the US [3•]. Hence, Kaposi's sarcoma remains an important cause of morbidity among HIV-infected individuals in the US and other developed nations. In sub-Saharan Africa, rates of HIV and HHV-8 coinfection are much higher than in developed countries, as is the incidence of Kaposi's sarcoma. Parkin [4•] has estimated that of 66 200 Kaposi's sarcoma cases worldwide in 2002, 58 800 occurred in sub-Saharan Africa, where Kaposi's sarcoma is among the most common of all diagnosed malignancies. Whitby *et al.* [5•] recently provided evidence to support the conjecture that exposure to natural products found in the African environment might account, at least in part, for higher HHV-8 reactivation rates, leading to higher rates of seroprevalence, higher viral loads and higher viral transmission rates in hyperendemic regions.

Here, we review recent progress in understanding the mechanisms underlying Kaposi's sarcoma pathogenesis

and the implications of these findings for the development of therapeutic strategies that target these mechanisms.

Advances in understanding the molecular underpinnings of Kaposi's sarcoma

KSHV is necessary for Kaposi's sarcoma development and is capable of altering the signaling properties of endothelial cells. KSHV-infected primary endothelial cultures show spindle cell-like morphology and extended proliferation capacity. KSHV encodes novel proteins as well as viral homologs of human proteins known to be involved in signaling and cancer; these include a cyclin homolog viral cyclin (vCyc)/orf72, a viral interleukin-6 homolog, chemokine homologs (viral macrophage inflammatory protein-1/2), a viral G-protein-coupled receptor (vGPCR), a viral CD200 homolog, a viral BCL-2, viral interferon regulatory factors and a FLICE inhibitory protein (vFLIP/orf71) homolog. Furthermore, viral proteins use conserved motifs to mimic cellular proteins, e.g. K1, which uses immunoreceptor tyrosine-based activation motifs to mimic receptor signaling.

The driving forces behind endothelial lineage tumors are different than those for other solid tumors. Kaposi's sarcoma seems to rely less on mutational activation of oncogenes or genetic inactivation of common tumor suppressor genes, and more on epigenetic changes and viral genes that modulate growth-stimulatory signaling pathways, in particular the Akt/mammalian target of rapamycin (mTOR) axis. The KSHV GPCR homolog orf74 and the viral K15 and K1 proteins induce ligand-independent signaling events that lead to transformation in culture and induction of progrowth cytokines, such as vascular endothelial growth factor (VEGF)-1 through Akt signaling [6•,7•], and induce expression of matrix metalloproteinases (MMPs), enzymes involved in the destruction of basement membrane and required for tumor invasion, metastasis and angiogenesis [2,8•].

Signaling kinases, including c-kit, the VEGF receptor and the platelet-derived growth factor receptor are upregulated, but not mutated, in Kaposi's sarcoma. This leads to the secretion of proangiogenic growth factors, which are responsible for the proliferative neovasculature that is a distinctive histologic feature of Kaposi's sarcoma. To date, however, attempts to target these kinases and growth factors in clinical trials have met with mixed results.

The Akt/mTOR signaling pathway has emerged as a promising new target in Kaposi's sarcoma. Akt is among the most frequently activated kinases in human cancer. It is negatively regulated by the PTEN (phosphatase and tensin homolog deleted on chromosome 10) tumor suppressor protein. Akt is an activating kinase for mTOR (through tuberous sclerosis complex-1/2, as well as directly). Stallone *et al.* [9] showed that biopsies of Kaposi's sarcoma tumors from renal allograft recipients expressed high levels of VEGF, the VEGF receptor (Flk-1/KDR), and phosphorylated Akt and p70S6 kinase, enzymes in the signaling pathway targeted by rapamycin. Sodhi *et al.* [6•] showed that cell lines expressing the HHV-8 vGPCR and vascular tumors that developed in vGPCR transgenic mice showed upregulated Akt/mTOR signaling and were susceptible to inhibition by rapamycin. The Dittmer laboratory has recently demonstrated that KSHV-associated primary effusion lymphoma (PEL) cells also were uniquely susceptible to inhibition by rapamycin [10•] and recently repeated these observations in a tumor model of Kaposi's sarcoma (unpublished observation). Inhibition of mTOR in Kaposi's sarcoma or PEL cells resulted in reduced protein synthesis of interleukin-6, interleukin-10 and VEGF, among others.

The p53 tumor suppressor gene is rarely muted in Kaposi's sarcoma [11], suggesting that epigenetic changes induced by viral oncogenes (LANA) or Hdm-2 overexpression inactivate p53 to allow continued cell proliferation. Yet, when induced and activated, the fully functional p53 can overcome these restrictions. This may explain the success of DNA-damaging agents such as liposomal doxorubicin in inducing Kaposi's sarcoma regression [12]. KSHV-associated PEL cell lines were shown to be uniquely sensitive to Nutlin-3, an Hdm2 antagonist that activates p53 [13•]. Recently, elegant mouse models have confirmed that reexpression of p53 in p53 null tumors also resulted in apoptosis or senescence, depending on the tumor type [14,15,16••]. These observations imply that tumors that eliminate wild-type p53 function by deletion or epigenetic inactivation rather than overexpression of a dominant-negative p53 mutant will become susceptible to p53 restoration and activation. Hence, one can hypothesize that Kaposi's sarcoma would be similarly responsive to p53-activating drugs.

The KSHV vCyc is a homolog of cellular cyclin D. Like human cyclin D, vCyc overexpression can drive cell proliferation by activating the cyclin-dependent kinases (Cdks), Cdk4 and Cdk6. Unlike human D-type cyclins, vCyc is resistant to the action of Cdk inhibitors, such as $p16^{ink4a}$, $p21^{Cip1}$ and $p27^{Kip}$ [17]. As Cdks are 'drugable' proteins, this offers a rationale for evaluating Cdk inhibitors against Kaposi's sarcoma. Most Cdk inhibitors target the ATP-binding site. Typically they show little selectivity against individual Cdk–cyclin complexes, which is an advantage as the vCyc–Cdk4 and vCyc–Cdk6 complexes, as expected, differ from cellular Cyc–Cdk complexes. Cdk inhibitors such as roscovitine can inhibit the replication of many herpesviruses [18–22], but it is unclear how inhibition of KSHV replication affects Kaposi's sarcoma tumorigenesis. There is at least the

possibility that inhibiting Cdks, which was recently shown to be a natural, novel function of vGPCR [23•], may lead to abortive virus replication and increased tumorigenesis. The situation has become even more complicated, as Cdk-independent functions of viral cyclins have been discovered [24•]. The role of these Cdk-independent activities in Kaposi's sarcoma tumorigenesis is not known.

Nuclear factor (NF)-κB is central to the biology of many tumors as it has significant growth promoting and antiapoptotic functions. NF-κB signaling also has an important role in Kaposi's sarcoma and even more so in KSHV-associated lymphomas. KSHV induces sustained NF-κB signaling upon de-novo infection of endothelial cells [25] and is required for latency of the murine KSHV homolog, MHV-68 [26•]. In PEL cell lines, disruption of NF-κB signaling by treatment with Bay 11-7082 or bortezomib leads to rapid cell death in culture [27–29]. Similar preclinical studies of NF-κB inhibitors have not yet been performed in Kaposi's sarcoma, as suitable culture and animal models have only recently been established. Nevertheless, since the inferences from PEL are encouraging and multiple inhibitors that broadly target NF-κB are entering clinical trials for other tumors, similar trials of NF-κB inhibitors could be considered for Kaposi's sarcoma.

Clinical trials

The growing understanding of the molecular events involved in Kaposi's sarcoma development has provided a basis for a number of early-phase clinical trials. Although relatively few such trials have been completed and published, a stronger basis for currently accruing and future clinical trials now exists that is based both on our understanding of Kaposi's sarcoma pathogenesis and on the development of agents with novel mechanisms of action.

Several clinical trials have targeted the angiogenic milieu associated with Kaposi's sarcoma with mixed results. IM862, a synthetic dipeptide that showed angiogenesis inhibitory activity in preclinical models and promising results in phase I and phase II clinical trials, proved ineffective in Kaposi's sarcoma when tested in a randomized, phase III, placebo-controlled trial [30]. More promisingly, a pilot study of imatinib mesylate (Gleevec), which targets c-kit and platelet-derived growth factor receptor signaling, resulted in partial clinical and histologic regression of cutaneous Kaposi's sarcoma in five of 10 patients [31], and a confirmatory phase II study is in progress by the AIDS Malignancy Consortium (AMC). A recent study in chronic myelogenous leukemia cells showed that responsiveness to imatinib was dependent upon the presence of wild-type p53, whereas p53 inactivation impeded the response [32]. This provides a tempting parallel to the experience with imatinib in Kaposi's sarcoma, but it is not known whether p53 inactivation explains those cases of Kaposi's sarcoma in which imatinib is inactive or loses efficacy.

As noted above, various MMPs are overexpressed in Kaposi's sarcoma lesions [2,8•] and contribute to the angiogenic milieu. Dezube *et al.* [33•] recently reported the results of a randomized, phase II AMC trial in 80 patients with AIDS-associated Kaposi's sarcoma of two doses of COL-3, an orally bioavailable, chemically modified tetracycline that inhibits MMP-2 and -9, and shows angiogenesis- and tumor-inhibitory activity in preclinical models. The lower dose (50 mg/day) induced a higher response rate than the higher dose (100 mg/day), 41 vs. 29%, respectively, and was better tolerated. Although plasma levels of MMP-2 and -9 declined overall, the decrease did not correlate with Kaposi's sarcoma response status.

Angiogenesis inhibitory activity has also been ascribed to interleukin-12, a cytokine that exerts a variety of effects of potential relevance to the treatment of malignancy. Interleukin-12 can promote T helper 1-type T cell development, increase cytotoxic T cell and natural killer cell activity, and induce the production of interferon (IFN)-γ, which in turn inhibits angiogenesis via induction of inducible protein-10 and monokine induced by IFN-γ (Mig) [34•]. A phase I/II trial of recombinant interleukin-12 was conducted by Little *et al.* [34•], who treated 34 patients with AIDS-associated Kaposi's sarcoma with twice-weekly subcutaneous doses ranging from 100 to 625 ng/kg. The maximum tolerated dose was 500 ng/kg, and adverse events included influenza-like symptoms, depression, arthralgias, hemolytic anemia and transaminase elevations. At doses of 300 ng/kg or more, 17 of 24 patients whose response to treatment could be evaluated showed complete (four patients) or partial (13 patients) Kaposi's sarcoma regression. Of interest, three patients whose tumors eventually regressed during interleukin-12 treatment initially showed tumor progression, but were nonetheless continued on interleukin-12. Also of interest is the long median time to first response (18 weeks, range 6–56) and the very long time required to achieve complete response, which ranged from 68 to 253 weeks. Although elevated serum levels of interleukin-12, IFN-γ and inducible protein-10 were observed in this study, which of the many potential mechanisms of action of interleukin-12 was responsible for the observed tumor regressions was not further defined.

IFN-α has long been known to be capable of inducing tumor regression in a subset of patients with AIDS-associated Kaposi's sarcoma and, like interleukin-12, its mechanisms of action are diverse, but include inhibition of angiogenesis. Most of the published experience with IFN-α in Kaposi's sarcoma has been in patients treated in

the 1980s and early 1990s who received IFN-α without concomitant antiretroviral therapy or in combination with single nucleoside reverse transcriptase inhibitors. In a phase I AMC study recently reported by Krown *et al.* [35•], escalating daily subcutaneous doses of recombinant IFN-α2b were administered to successive cohorts of patients with AIDS-associated Kaposi's sarcoma who were receiving concomitant treatment with protease inhibitor-based HAART. This trial established 5×10^6 IU of recombinant IFN-α2b as the maximum tolerated dose in combination with protease inhibitor-based HAART and although Kaposi's sarcoma regression was observed, the study included only 14 patients and was not designed to estimate the response rate at the maximum tolerated dose nor was the mechanism of Kaposi's sarcoma regression investigated. A limited analysis failed to show clearance of KSHV from plasma or peripheral blood mononuclear cells, even among patients whose Kaposi's sarcoma regressed.

Constitutive activation of the Akt/mTOR signaling pathway in Kaposi's sarcoma lesions has provided a rationale for the therapeutic application of drugs that inhibit this pathway. In 1995, Stallone *et al.* [9] made the remarkable observation that of 15 renal allograft recipients who developed cutaneous Kaposi's sarcoma, all showed complete regression of their lesions when their immunosuppression was changed from a cyclosporine-based regimen to single-agent rapamycin (sirolimus), which unlike cyclosporine inhibits mTOR. Notably, none of the patients rejected their allograft after the immunosuppressive regimen was modified [9], thus separating the immunosuppressive effects of rapamycin from its antitumor activity. Since then similar successes in the transplant setting have been reported by others, as well as some failures [36••]. Several studies have also pointed to a role for rapamycin in the prevention of cancers in renal allograft recipients, but the extent to which this applies specifically to Kaposi's sarcoma is unclear [37•,38•]. The strong evidence in support of a role for mTOR activation in the development of Kaposi's sarcoma and the demonstrated potential for TOR inhibitors to cause Kaposi's sarcoma regression has led the AMC to initiate a clinical trial of rapamycin in patients with AIDS-associated Kaposi's sarcoma. The finding that inhibition of constitutive mTOR activation in tumor cells can result in disruption of feedback downregulation of receptor tyrosine kinase signaling and lead to Akt activation [39••] suggests that combining mTOR inhibition with inhibitors of Akt activation may ultimately prove more therapeutic. The use of such combinations is further supported by the observation that Akt inhibitors also block KSHV K1 and vGPCR-associated endothelial cell proliferation [2,40].

HAART has resulted in both a decreased incidence of Kaposi's sarcoma and to regression of established Kaposi's sarcoma lesions in a subset of patients, but the mechanisms responsible for HAART-induced Kaposi's sarcoma regression are not well understood. There remains controversy about the relative contributions of direct effects of antiviral agents on tumor growth vs. more general stimulation by HAART of immune system-mediated mechanisms of Kaposi's sarcoma regression and inhibition of Tat- and cytokine-mediated stimulation of Kaposi's sarcoma growth. Recently published studies in other tumor types have provided insights into potentially relevant mechanisms by which HIV protease inhibitors may induce Kaposi's sarcoma regression. In a hepatocellular carcinoma model, indinavir was shown to inhibit MMP-2 proteolytic activation, inhibit angiogenesis and induce apoptosis [41]. Nelfinavir was shown to inhibit in-vitro growth of melanoma cells by a mechanism that involved inhibition of Cdk2 through proteasome-dependent degradation of Cdc25A phosphatase, leading to cell cycle arrest [42]. Ritonavir was shown to inhibit breast cancer cell line growth, at least in part by binding to and partially inhibiting the chaperone function of heat shock protein 90, leading to depletion of Cdk2, 4 and 6, cyclin D1, and Akt [43•]. The role of any of these mechanisms in inducing Kaposi's sarcoma regression is unclear, as a retrospective analysis has shown that the clinical response of Kaposi's sarcoma to HAART was associated with effective suppression of HIV, but was independent of whether a protease inhibitor-based or nonnucleoside reverse transcriptase inhibitor-based regimen was administered [44••]. Clinical trials to evaluate indinavir's antitumor activity are ongoing in both classic and AIDS-associated Kaposi's sarcoma [45,46].

A number of other possibilities currently exist for clinical trials in Kaposi's sarcoma using agents that are Food and Drug Administration-approved for treatment of other cancers and which are based on our current understanding of Kaposi's sarcoma pathogenesis. Several such studies are in progress or under consideration. These include trials of the multitargeted receptor tyrosine kinase inhibitors, sorafenib and sunitinib; a monoclonal antibody to VEGF, bevacizumab; the proteasome inhibitor, bortezomib, which inhibits NF-κB; histone deacetylase inhibitors, which can reverse herpesvirus latency and induce apoptosis of infected cells [47•]; and Cdk inhibitors, which in addition to inhibiting cell cycle progression, also inhibit VEGF production [48] and replication of both HHV-8 and HIV. HIV inhibition occurs via inhibition of P-TEFb, which is a required cellular cofactor for the HIV transactivator protein, Tat [49], which itself has been shown to be a growth factor for Kaposi's sarcoma cells *in vitro* [50•].

Conclusion

Recent progress has been made in understanding the molecular mechanisms by which KSHV can induce

Kaposi's sarcoma lesions and in developing more effective therapeutic strategies for Kaposi's sarcoma. While the results of some of these clinical trials are promising, treatments for Kaposi's sarcoma are not invariably effective and we currently do not understand enough about the angiogenic phenotype of Kaposi's sarcoma lesions to rationally select the agents that will prove most effective. The complexity of Kaposi's sarcoma biology suggests that effective treatment strategies will require a combination of agents that affect multiple pathways in Kaposi's sarcoma pathogenesis.

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