**EDITORIAL**

Kaposi’s Sarcoma and Kaposi’s Sarcoma-Associated Herpesvirus (Human Herpesvirus 8): Where Are We Now?

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Kaposi’s sarcoma-associated herpesvirus (KSHV) is the eighth and most recently described human herpesvirus (HHV8). During the past 3 years, accumulating evidence leaves little doubt that this virus is the infectious cause of Kaposi’s sarcoma (KS). An infectious etiology for KS has been sought for over 3 decades, and a number of viruses and bacteria have been proposed to be the “KS agent.” In each case, the proposed agent has been unable to explain the unusual epidemiology of this tumor.

KSHV, on the other hand, appears to be a nonubiquitous herpesvirus that is present in virtually all KS lesions, regardless of the patient’s underlying human immunodeficiency virus 1 (HIV) status. Serologic studies show that the prevalence of KSHV infection in various geographic and risk-group populations parallels the incidence of KS in these populations. For example, the rate of HIV-negative KS follows a pattern where the tumor is least common in the United States and the U.K., more common in Italy and other Mediterranean countries, and most common in Central African countries. The KSHV seroprevalence among blood donors and other control populations follows this same geographic pattern, with less than 5%–10% of U.S. blood donors being KSHV seropositive, whereas the infection rate among persons from Kampala, Uganda, can exceed 50% (1,2). Similarly, several studies (see (3,4)) have found approximately 30% seroprevalence rates, using a variety of antigens, among homosexual men without KS but far lower infection rates among individuals in other HIV risk groups who also have lower rates of developing acquired immunodeficiency syndrome-related KS (AIDS-KS).

Longitudinal studies provide the strongest evidence that KSHV is causal for KS in that both polymerase chain reaction (PCR)-based detection of KSHV DNA in peripheral blood (5) and antibody seroconversion studies (6) show that KSHV infection occurs before the development of the tumor and is highly predictive for tumor development. More recently, Parravicini et al. (7) identified a kidney transplant recipient who was infected from an organ that was received from a living, related, asymptomatic, KSHV-seropositive donor. This patient subsequently developed both Castleman’s disease and KS, two apparent manifestations of KSHV infection in the immunocompromised host. Despite this documented case of allograft transmission, most transplant patients who develop KS are already infected before the transplantation, and their disease results from iatrogenic immunosuppression—not from new infection (7).

Epidemiologic studies now provide a fairly coherent and clear picture of the patterns of KSHV infection leading to KS development and show that KSHV largely fulfills Hill’s criteria for causality (8). Despite the good fortune of finding that the epidemiology of KS is tractable, we still do not know precisely how the virus is transmitted or to whom. The detection of KSHV infection in patients with multiple myeloma (9) and in other populations at low risk for KS may either represent technical red herrings or tell us that the epidemiology of this virus is more complicated than the initial studies have led us to assume.

One of the most important questions that now needs to be addressed is how KSHV initiates the pathogenic events resulting in KS tumor formation. Before the discovery of the virus, KS was largely thought to be a hyperplastic process driven either by endogenous cytokine dysregulation or by hypersecretion of HIV tat protein in AIDS-KS lesions (10,11). However, as Davis et al. (12) show in this issue of the Journal, the majority of the spindle cells in KS tumors are infected by KSHV and contain viral messages encoding a cellular D-type cyclin homologue (v-cyclin). The widespread distribution of these KSHV-encoded cyclin transcripts in the context of restricted expression of other viral transcripts in KS spindle cells is consistent with v-cyclin being a latent gene. This finding, in turn, supports the notion that the virus is in a latent state in the majority of KS spindle cells. The first indication that most KS tumor cells are infected with the virus was obtained using in situ PCR (13), a technique that has been criticized for its experimental variability. However, this result was confirmed by Staskus et al. (14) using in situ hybridization for KSHV T0.7 (kaposin) messenger RNA and by Rainbow et al. (15) who demonstrated protein expression from orf73, which encodes the latency-associated nuclear antigen (LANA), in nearly all KS spindle cells. Davis et al. (12) confirm and extend these findings to v-cyclin.

In contrast to kaposin and LANA, whose functions are not
known, the role of v-cyclin can be inferred from its sequence similarity to cellular cyclins. Cyclins are a family of proteins that regulate control of the cell cycle and DNA replication [see (16) for a review]. They function by binding to and stimulating specific cyclin-dependent kinases (cdks) that phosphorylate other proteins involved in cell cycle regulation. Subtypes of cyclins have been defined according to where they act in the cell cycle. The D-type cyclins, which have highest homology to the KSHV-encoded cyclin, are induced by growth factor stimulation and act during the mid-to-late G1 phase of the cell cycle. Constitutive expression of D-type cyclins in tissue culture cells results in a shortened G1 interval and growth factor-independent cellular expression of D-type cyclins in tissue culture cells results in a shortened G1 interval and growth factor-independent cellular proliferation without differentiation. D-type cyclins preferentially interact with cyclin-dependent kinases (cdks) that phosphorylate the retinoblastoma tumor suppressor protein (pRb), which controls entry into S phase. In its hypophosphorylated form, pRb blocks cells in the G1 phase by binding to a variety of proteins that include a family of transcription factors collectively known as E2F. Phosphorylation of pRb causes the release of E2F, a step necessary for the transcription of genes required for DNA synthesis and for cell growth control. Inhibition of pRb is therefore a critical step in cell growth dysregulation and may be essential for tumor development. This simplified description of the pRb pathway identifies several points that can be altered to cause dysregulation of cell cycle control. Mutations in pRb and overexpression of cyclins are examples of abnormalities found in a variety of tumors and cell lines that disrupt normal control of the pRb pathway.

The importance of the pRb tumor suppressor pathway is underscored in the requirement for its inactivation by a variety of phylogenetically diverse tumor viruses. Simian virus 40 T antigen, adenovirus E1A oncoprotein, and papillomavirus E7 oncoprotein all bind hypophosphorylated pRb to release cells from pRb-enforced growth arrest. Herpesvirus saimiri (HVS) and Epstein-Barr virus (EBV), two tumor-forming gammaherpesviruses related to KSHV, do not directly inhibit pRb but appear to alter cyclin activity to inhibit pRb indirectly. HVS, like KSHV, encodes a functional human cyclin homologue in its genome (17,18), whereas EBV induces cellular cyclins in infected cells (19). In these herpesviruses, the contribution of cyclin dysregulation toward promoting neoplastic transformation has not been extensively explored. Isolated gene studies (20–22) of the KSHV v-cyclin demonstrate that the encoded protein is capable of inducing pRb phosphorylation, primarily through cdk-4 activation, and can release cells from the growth-proliferation blockade induced by pRb expression. Unlike the cellular D-type cyclins, KSHV v-cyclin can directly phosphorylate of histone H1 as well, demonstrating that it has broader substrate specificity than the cellular D-type cyclins. It is reasonable to expect that KSHV-infected spindle cells expressing v-cyclin undergo endogenous proliferation due to pRb inactivation. Whether this inactivation results in polyclonal tumor cell proliferation or monoclonal transformed cell outgrowth remains to be determined. Furthermore, a critical role for cytokines in maintaining the tumor phenotype is not excluded, but the findings of Davis et al. provide a plausible pathogenic mechanism in which some portion of the signals driving KS spindle cell proliferation comes from an endogenous (intracellular) viral source.

It is unlikely that v-cyclin expression alone induces the KS spindle cell tumor phenotype, but it is probably only one important component of the process of tumor formation. The transparency of the KSHV genome provides clues as to which other KSHV genes should be examined for their role in KS tumorigenesis. There is an interesting parallel between homologue genes encoded by KSHV and cellular genes induced by EBV infection [see Fig. 1 and (23) for a more complete description], suggesting that both viruses modify similar signaling pathways. Some genes, such as v-interleukin 6 (v-IL-6), are not expressed in KS lesions but may have activity in other tissues, particularly in infected lymphocytes. The search for critical genes that are central to KS tumorigenesis now can be undertaken by expression studies, like the one by Davis et al., and by functional studies of the homologue genes encoded by KSHV.

References


