Addressing Controversies Over Kaposi’s Sarcoma

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Kaposi’s sarcoma has emerged from being a rarity to being the most important neoplasm in many sub-Saharan countries. Most investigators involved in Kaposi’s sarcoma research now agree that the gammaherpesvirus human herpesvirus 8 (HHV8), also called Kaposi’s sarcoma-associated herpesvirus (KSHV), is central in the pathogenesis of this disease (1,2). Molecular and seroepidemiologic studies (3,4) have confirmed the association between HHV8 and Kaposi’s sarcoma. However, the role of HHV8 in the initiation and maintenance of proliferation of Kaposi’s sarcoma tumor cells (spindle cells) remains unclear. Before the discovery of HHV8 (5), it was thought that cellular cytokines, growth factors, and the human immunodeficiency virus-1 (HIV-1) Tat protein initiate and promote the growth of Kaposi’s sarcoma spindle cells (6). The fact that the incidence of Kaposi’s sarcoma is much higher among HIV-1-infected individuals than among iatrogenic immunosuppressed patients probably reflects the prevalence of HHV8 in different populations, rather than indicates that HIV-1 itself plays a role. Kaposi’s sarcoma, like HHV8, is rare in HIV-positive, injecting drug users and in patients with hemophilia (3). However, rapidly progressive Kaposi’s sarcoma affecting extensive parts of the skin, oral and genital mucosae, and internal organs is seldom seen in HIV-negative patients, even in those iatrogenically immunosuppressed for prolonged periods. This observation favors a synergistic role for HHV8 and for HIV-1 in promoting growth of Kaposi’s sarcoma spindle cells.

Previous studies (6,7) have pinpointed the Tat protein of HIV-1 as being an angiogenic factor that can induce the expression of a cascade of cytokines involved in the pathogenesis of Kaposi’s sarcoma. In this issue of the Journal, Prakash et al. (8) show that, when the human Kaposi’s sarcoma SLK cell line was injected subcutaneously into HIV-1 Tat transgenic CD4+ T-cell-depleted male mice, the rate of tumor growth was substantially faster than that in non-Tat transgenic animals. Furthermore, transcripts for various cytokines previously shown to be induced by Tat were increased in the tumors of the Tat transgenic animals. The SLK cell line was originally established from a mucosal Kaposi’s sarcoma lesion of an HIV-negative kidney transplant patient (9). Although this cell line expresses, like Kaposi’s sarcoma spindle cells, markers associated with an endothelial origin, the SLK cells are, unlike in situ Kaposi’s sarcoma spindle cells, negative for HHV8. HHV8 is latency present in the vast majority of Kaposi’s sarcoma spindle cells in established lesions (10), and the growth characteristics of SLK cells, therefore, might not be typical of Kaposi’s sarcoma spindle cells. However, the notable finding of the article by Prakash et al. is that tumor cells grow faster in vivo in the presence of circulating HIV-1 Tat. We predict that similar findings might be obtained in Tat transgenic mice injected with tumor cells other than Kaposi’s sarcoma spindle cells. Thus, the tumor-promoting effects of HIV-1 Tat in HIV-1-infected individuals might be important across a broader spectrum of malignancies and might not be restricted to Kaposi’s sarcoma.

The fact that the incidence of Kaposi’s sarcoma is higher in African countries where HIV-1 is prevalent than in countries where HIV-2 is more common, despite similar prevalence of antibodies to HHV8 (11), has argued in favor of functional differences between HIV-1 and HIV-2 Tat proteins (12). Although the increased incidence in HIV-1-infected individuals of various neoplasia, including Kaposi’s sarcoma, lymphoma, and squamous cell carcinoma, is well documented (13), we are not aware of definitive cancer statistics from HIV-2-prevalent regions. HIV-1 Tat could affect indirectly tumor cell proliferation via the induction of cellular growth and angiogenic factors and/or directly via the activation of transcription regulators like NF-κB. Prakash et al. (8) did not demonstrate increased angiogenesis in the Tat transgenic tumors compared with the Tat-negative ones, suggesting that Tat-induced angiogenesis might not be that important in vivo. An interesting study would be to look at the growth characteristics of SLK cells, other Kaposi’s sarcoma cells, and other tumor cell lines in HIV-2 compared with HIV-1 Tat transgenic mice.

In other experimental models, HIV and inflammatory cytokines also appear to influence HHV8. In lymphoma cells latently infected with HHV8, HIV activates HHV8 infection (14). HHV8 replication is also activated by HIV-1 Tat in lymphoma cells and in peripheral blood mononuclear cells (15). In addition, interferon gamma reactivates HHV8 lytic replication in lymphoma cells (16). Interferon gamma is present in Kaposi’s sarcoma

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lesions and cooperates in vitro with HIV-1 Tat to stimulate endothelial cell growth (17).

If HIV-1 Tat and inflammatory cytokines are involved in the pathogenesis of Kaposi’s sarcoma, we may predict that early lesions are polyclonal hyperplasias rather than clonal cancers. This argument is supported by the finding that only a fraction of tumor cells in early Kaposi’s sarcoma lesions is infected by HHV8, whereas HHV8 is present in the vast majority of spindle cells of late-stage nodular lesions (10). By examining the X-chromosome inactivation pattern of the human androgen receptor gene in women with Kaposi’s sarcoma, two groups of investigators (18,19) have shown that some Kaposi’s sarcoma lesions are polyclonal, whereas other lesions, especially advanced lesions, can be monoclonal.

In another article appearing in this issue of the Journal, Judde et al. (20) expanded a study first explored by the discoverers of HHV8 (21). Judde et al. investigated HHV8 clonality within tumors by looking at the size heterogeneity of HHV8-fused terminal repeats (TRs). This assay has been previously used to demonstrate that certain Epstein-Barr virus (EBV)-associated tumors are monoclonal (22). However, the TR region of HHV8 is much larger, and rearrangements, therefore, might occur, skewing data toward oligoclonality or polyclonality. Judde et al. (20) showed that HHV8 is monoclonal in a number of nodular Kaposi’s sarcoma lesions, indicating that HHV8 was present before the expansion of a tumor clone of Kaposi’s sarcoma spindle cells. In other advanced lesions, they demonstrated more than one dominant band, suggesting the outgrowth of individual clones within one lesion. In their study, they did not address the cellular clonality in early or multiple lesions. Their data, however, support the hypothesis that early lesions are polyclonal and cytokine driven, with only a few cells infected by HHV8, whereas advanced lesions represent monoclonal or oligoclonal infected populations of spindle cells because of the growth advantage provided by latent HHV8 proteins (10,19).

Jude et al. (20) also investigated the clonality of HHV8 in the lymphoproliferative disorders associated with this virus: primary effusion lymphoma and multicentric Castleman’s disease. Not surprisingly, two of four primary effusion lymphomas showed monoclonal HHV8 bands (20), confirming studies of immunoglobulin (Ig) gene rearrangements (23). In contrast, their results suggest that HHV8-associated multicentric Castleman’s disease is polyclonal (20). However, HHV8 is present in B-cell plasmablasts scattered usually in the mantle zone of germinal lymph follicles affected by Castleman’s disease (10). Since HHV8 is also present in infiltrating and circulating lymphocytes, the study of clonality, using viral TR or cellular Ig rearrangements as markers, might be misleading without using laser capture microdissection techniques to examine the neoplastic plasmablasts in particular. Furthermore, all of the HHV8-infected plasmablasts in Castleman’s disease show lambda light chain restriction (24). If these cells are not, therefore, monoclonal, but polyclonal, it would indicate a fundamental difference in the response to HHV8, or of viral tropism, for B cells expressing kappa versus lambda light chains.

A role for HIV-1 in the pathogenesis of Kaposi’s sarcoma is supported by the observations that Kaposi’s sarcoma can rapidly resolve with highly active antiretroviral therapy (HAART). Whether these responses are purely due to a restoration of cellular immunity against HHV8 or due to the lower circulating HIV-1 load is not yet known. In contrast, HHV8-positive Castleman’s disease does not often resolve and can, despite HAART, progress to fatal lymphoma (24,25). These differential responses may reflect the behavior of cytokine-driven neoplasia compared with clonal tumors.

References


