Human Herpesvirus 8 and Cancer

Valerie Beral, Robert Newton, Freddy Sitas

In 1994, Chang, Moore, and colleagues (1) reported that they had discovered DNA sequences of a new herpesvirus in Kaposi’s sarcoma tumor tissue. The new virus, known as Kaposi’s sarcoma herpesvirus or human herpesvirus 8 (HHV8), is now widely believed to be a necessary cause of Kaposi’s sarcoma [(2); reviewed in (3)]. The prevalence of antibodies against HHV8 varies substantially across populations, and there is a close association worldwide between seroprevalence rates of anti-HHV8 antibodies and the incidence of Kaposi’s sarcoma. Kaposi’s sarcoma is extremely rare in northern America and northern Europe (except among homosexual men with acquired immunodeficiency syndrome [AIDS]), is more common in southern Europe, and is most common of all in Africa (4–8). Likewise, the proportion of adults in the general population with antibodies against HHV8 ranges from fewer than 5% in northern America and northern Europe to around 10% in southern Europe and more than 20% in black Africans [reviewed in (3); (9)]. In the United States and Europe, more than 30% of human immunodeficiency virus-1 (HIV)-infected homosexual men have been found to have antibodies against HHV8 [reviewed in (3); (9–12)].

In this issue of the Journal, Rezza et al. (12) report that, in 366 Italian subjects known to have become infected with HIV, 38.3% also had antibodies against HHV8. During a 10-year follow-up period, nearly 30% of those who were co-infected with HIV and HHV8 developed Kaposi’s sarcoma, the risk being increased in individuals with relatively high titers of anti-HHV8 antibodies (12). The findings of Rezza et al. echo results published earlier this year from South Africa (13), where the risk of Kaposi’s sarcoma increased with increasing anti-HHV8 antibody titer, although at each titer the risk was considerably greater in HIV-seropositive than in HIV-seronegative subjects—the odds ratios at the highest level of anti-HHV8 antibody titer were 12 and 1682, respectively, in HIV-seronegative and HIV-seropositive subjects (Table 1).

Recent findings, therefore, suggest that, even though HHV8 may be a necessary cause of Kaposi’s sarcoma, other factors, such as co-infection with HIV and anti-HHV8 antibody titers, are crucial in determining who develops Kaposi’s sarcoma and who does not. Co-infection with HIV leads to an enormous increase in the incidence of Kaposi’s sarcoma, and the effect of HIV appears to be independent of anti-HHV8 antibody levels (13). For other virus-related cancers, persistent and active viral infection is often vital, and it is possible that HIV infection might encourage the persistence of what would otherwise have been a self-limiting new infection by HHV8 or lead to the reactivation of latent HHV8 infection. Other mechanisms, such as HIV-related immune dysregulation or the effect of its transactivation (Tat) protein (14), may also be involved, but as yet there is little direct evidence to explain why co-infection with HIV greatly enhances the development of Kaposi’s sarcoma.

### Table 1. Odds ratio for Kaposi’s sarcoma in relation to human immunodeficiency virus-1 (HIV) infection and median anti-human herpesvirus 8 (anti-HHV8) antibody titer in black South Africans*

<table>
<thead>
<tr>
<th>Antibody Titer</th>
<th>Odds Ratio (95% confidence interval)</th>
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</thead>
<tbody>
<tr>
<td>HIV seronegative, median anti-HHV8 antibody titer</td>
<td></td>
</tr>
<tr>
<td>&lt;1 : 100</td>
<td>1.0 (referent)</td>
</tr>
<tr>
<td>1 : 200</td>
<td>1.5 (0.3–7.8)</td>
</tr>
<tr>
<td>1 : 51 200</td>
<td>6.2 (1.6–24.2)</td>
</tr>
<tr>
<td>1 : 204 800</td>
<td>12.0 (2.1–68.2)</td>
</tr>
<tr>
<td>HIV seropositive, median anti-HHV8 antibody titer</td>
<td></td>
</tr>
<tr>
<td>&lt;1 : 100</td>
<td>10.8 (2.9–40.6)</td>
</tr>
<tr>
<td>1 : 200</td>
<td>48.1 (7.7–300)</td>
</tr>
<tr>
<td>1 : 51 200</td>
<td>62.2 (18.0–214)</td>
</tr>
<tr>
<td>1 : 204 800</td>
<td>1682 (390–7253)</td>
</tr>
</tbody>
</table>

*Adapted from Sitas et al. (13).

That high anti-HHV8 antibody titer is strongly related to Kaposi’s sarcoma risk (irrespective of co-infection with HIV) suggests that increased expression of viral genes, perhaps through HHV8 viremia, may be relevant. Intriguing similarities are emerging between the effect of HHV8 in Kaposi’s sarcoma and the effect of the closely related human herpesvirus, the Epstein-Barr virus, in Burkitt’s lymphoma (15). In both situations, high antibody titer appears to be a key indicator of which infected individuals will go on to develop a tumor. Further exploration of these analogies may well hasten our understanding of the mechanisms of viral carcinogenesis in humans.

Over the last few years, HHV8 has been tentatively linked to a variety of conditions, other than Kaposi’s sarcoma. Molecular studies have consistently found HHV8 in association with some unusual lymphoproliferative disorders, primary effusion lymphoma and Castleman’s disease [reviewed in (3); (16)]. However, apart from these extremely rare malignancies, epidemiologic evidence indicates that HHV8 infection has little or no effect on common cancer types or sites, including cancer of the prostate, multiple myeloma, leukemia, and Hodgkin’s disease (13). In addition, Rezza et al. (12) report that HHV8 infection does not lead to an increased risk of AIDS-defining diseases, other than Kaposi’s sarcoma.

There are few instances in cancer research where our understanding of the pathogenesis of a human cancer has progressed

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as rapidly as it has for Kaposi’s sarcoma. Jaffe and Pellett (2) attributed this success to “the benefits gained from the synergy between epidemiologic and laboratory science.” New collaborative research on the natural history of HHV8 infection and on the pattern of antibody response to infection should continue to shed light on why only some people who have been infected by HHV8 go on to develop Kaposi’s sarcoma. At the same time, new information is likely to emerge about the way that HHV8 is transmitted. Although HHV8 can be transmitted from mother to child, by sexual contact, and via blood products (17–19), other, as yet unknown, modes of transmission are likely to predominate in Africa (13). Indeed, it is not yet known whether HHV8 can be spread through water or by oral–fecal contact, as the results of some epidemiologic studies of people with Kaposi’s sarcoma (20–22) have suggested. Ongoing collaboration between epidemiologists and laboratory scientists should ensure that the remarkably rapid advance in knowledge about HHV8 infection and Kaposi’s sarcoma continues into the future.

REFERENCES