Poor Specific T Cell Responses to Human Herpesvirus 8: A Key to Unleashing Kaposi Sarcoma?

Richard F. Little and Robert Yarchoan
HIV and AIDS Malignancy Branch, Center for Cancer Research, National Cancer Institute, Bethesda, Maryland

(See the article by Guihot et al., on pages 1078–88.)

Immune responsiveness to tumor antigens forms a conceptual framework for a broad field of research that can inform a wide range of studies of cancer pathogenesis and immunotherapy. The spectrum of translational clinical research studies in this area encompasses tumor vaccines, stem cell transplantation, and biologic therapies, such as the administration of immunomodulatory cytokines and monoclonal antibodies. Virus-induced tumors are of particular interest, because, by necessity, the virus provides exogenous antigens to which immune responses may be directed. In this issue of the *Journal of Infectious Diseases*, Guihot et al. have provided compelling data assessing measures of immune surveillance of human herpesvirus 8 (HHV-8; also called “Kaposi sarcoma [KS]–associated herpesvirus”) relative to KS [1]. The finding have the potential to stimulate further productive inquiry in this and related fields.

HHV-8 and a related γ-herpesvirus, Epstein-Barr virus (EBV), persist lifelong in the human host. These viruses promote the development of cancer, but overt malignancy occurs only in a minority of viral carriers. For this reason, carriers provide a natural platform on which investigators can explore the interactions between immune responses to viral or tumor antigens and disease manifestations. The mechanisms of viral escape from immune control and consequent oncogenesis are not fully understood. Building on previous work in this area [2–4], Guihot et al. used a number of short peptides to assess cellular immune responses to both latent and lytic viral gene products. The peptides included segments of latent nuclear antigen 1, K12, and K15 as well as 4 previously described HHV-8 epitopes, and the main measure was the frequency of interferon (IFN)-γ–producing T cells, as assessed by enzyme-linked immunospot assay. Comparisons were made among several groups of patients defined by the presence or absence of KS, HHV-8 infection, and HIV infection. Perhaps the most notable finding was that patients with KS had substantially decreased immune responses to HHV-8 antigens, compared with those in HHV-8–infected patients without KS, and that this difference persisted when subgroups matched for CD4 cell count were compared. Strikingly, HHV-8– and HIV–coinfected long-term nonprogressors without KS had more HHV-8–specific T cells than did HIV-uninfected patients with classic Mediterranean KS. These findings broaden our knowledge of the relationship between HHV-8 and KS and offer provocative concepts that may apply to other γ-herpesvirus–related tumors. Also, by defining new T cell epitopes of HHV-8, Guihot et al. have laid the groundwork for future studies.

For years, it has been recognized that various opportunistic tumors associated with HIV infection tend to occur below certain threshold CD4 cell counts and to be more common as CD4 cell counts decrease. On the surface, this concept appears to be challenged by the data presented by Guihot et al., whose patients with KS had poor specific T cell responses regardless of their CD4 cell count. It is possible that this, in part, reflects changes in the pattern of HIV-related complications associated with the use of highly active antiretroviral therapy (HAART) and the ability of HAART to effect substantial improvements in immune function. In the HAART era, it is clear that HHV-8– and EBV–related neoplasms occur across a wider spectrum of CD4 cell counts than was initially appreciated, and the concepts presented by Guihot et al. may help to unravel these relationships. Another possibility that may explain this seeming paradox is that CD4 cell count serves as a surrogate marker for the specific T cell
response to HHV-8 antigens, and the latter is the main factor that affects the development of KS. Additional studies will be needed to tease out these issues.

It is noteworthy that immune responses to both latent and lytic HHV-8 genes were diminished in patients with KS. Lytic replication of herpesviruses usually involves the death of the producing cell, and for this reason lytic genes have been considered relatively unimportant in herpesvirus-induced tumorigenesis. However, there is an increasing appreciation of the role that lytic genes play in tumors caused by EBV and HHV-8 [5–10]. Guihot et al.’s finding that a lack of T cell responses to HHV-8 lytic antigens is associated with KS is consistent with the concept that such genes are important in KS oncogenesis.

There is recent evidence that a virally encoded G protein–coupled receptor plays a key role in the development of KS [11], and it would be interesting to discover whether a lack of T cell responses to this gene is similarly associated with the development of KS. An intriguing possibility is that the IFN-γ produced by specific T cells may help to control KS by stimulating the generation of inducible protein 10, which inhibits signaling by this constitutively active receptor [12].

Guihot et al. failed to find an association between a T cell response to HHV-8 peptides and HHV-8 load in peripheral-blood mononuclear cells (PBMCs). This is an unexpected result if it is assumed that cytotoxic T cells affect KS by controlling HHV-8 replication. However, a similar phenomenon has been observed in the case of EBV-related posttransplantation lymphoproliferative disease, in which tumor burden does not correlate with viral load [13]. HHV-8 load may vary in different reservoirs in the body [14], and it is possible that certain viral populations targeted by the immune response are more important for the development of KS than the PBMC compartment assessed by Guihot et al.

The identification of key epitopes on these viruses may help to enable strategies for tumor immunization against both latent and lytic gene products and as a basis for investigations into both EBV and HHV-8. Targeted immune responses may also delay the development of KS or other HHV-8–related neoplasms in those already infected with the virus, as appears to be the case when HHV-8 infection precedes HIV infection [15]. An understanding of this process may also aid in the development and assessment of immunotherapeutic strategies for γ-herpesvirus–associated malignancies. For example, IL-12 has recently been shown to be active in KS [16], and it will be of interest to learn if it stimulates specific responses against HHV-8 antigens. Adoptive immunotherapy is effective in certain EBV-related lymphoproliferative diseases but generally not after clonal malignant transformation has occurred. Overcoming this barrier may be facilitated by the identification of additional targets and the genetic engineering of T cells to expand the range of immune responses to virus-associated tumors. Given that certain EBV- and HHV-8–associated tumors are often refractory to standard oncologic approaches, successful novel strategies would considerably advance therapy for these diseases. For example, current cytotoxic approaches to primary effusion lymphoma (PEL) are usually ineffective, and prognosis for this tumor is worse than that for most other AIDS-related lymphomas [17]. Immunotherapeutic approaches potentially informed by work such as that done by Guihot et al. could be explored in PEL and other virus-related cancers with poor prognoses.

References