EDITORIALS

Viral-Associated Neoplasms in Humans: Additional Clues

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Employing technical methods representing diverse ends of a large spectrum, Cleghorn et al. (1) and Lunardi-Iskandar et al. (2) have each developed models by which we may further elucidate the precise mechanisms of virally induced or associated neoplastic disease, as reported in this issue of the Journal. The study by Cleghorn et al. consisted of two large populations, one in Jamaica and the other in Trinidad. Using census reports, serosurvey data, and immunophenotype analysis of lymphoma tissues, incidence rates for human T-lymphotropic virus type I (HTLV-I)-associated T-cell lymphomas were ascertained in these two HTLV-I endemic regions. Of interest, while the overall incidence and epidemiologic characteristics of B-cell lymphomas were consistent with those reported in other areas of the world (demonstrating an increasing incidence with age and a higher age-specific rate for males), a different pattern of lymphomatous disease was demonstrated in those patients who had been infected with HTLV-I early in life. In these individuals, an inverse relationship between age and incidence of T-cell lymphoma was observed, with an equal distribution among the sexes. Also, sexual transmission of HTLV-I is more efficient from male to female, as demonstrated epidemiologically by a plateau in prevalence rates among males older than 40 years of age, although the prevalence of HTLV-I seropositivity continues to increase among females with increasing age. Despite this fact, the age-specific incidence of lymphoma among HTLV-I-infected persons overall is higher in males than in females. These data are consistent with the hypothesis that early infection by HTLV-I may be critical for the full development and expression of neoplastic disease, while sexually transmitted infection in adults may be "irrelevant" in this regard, as suggested by Cleghorn, et al. (1). While this hypothesis may be true in general, it is important to note the occurrence of adult T-cell leukemia/lymphoma among those who have been coinfected by HTLV-I and human immunodeficiency virus type 1 (HIV-1), with both infections presumably occurring via sexual contact in adult life (3,4). Thus, in the setting of HIV-related immunodeficiency, or in other types of immunocompromise (5), the possibility of sexually transmitted HTLV-I-induced tumorigenesis may be highly relevant and worthy of future study. Nonetheless, using large human populations, Cleghorn et al. (1) have provided a potential model in which to explore the mechanisms of oncogenesis, as well as mechanisms for the potential prevention of malignant disease, by preventing the early transmission of HTLV-I from mother to infant.

Lunardi-Iskandar et al. (2) have provided another model, with similar potential for understanding the precise steps required for full expression of malignant disease in humans. The method used in their work was more traditional, employing cells as opposed to human populations. Using large numbers of primary Kaposi's sarcoma (KS) cells derived from a pleural effusion, extensive depletion of coexisting T cells, B cells, monocytes/macrophages and fibroblasts, and absence of additional growth factors, a malignant cell line termed KS Y-1 was established. This line has now undergone more than 100 passages and remains stable. The KS Y-1 cell line appears to have fulfilled the criteria for malignancy in that 1) additional growth factors are not required; 2) an abnormal tetraploid karyotype was identified, which is identical to that demonstrated from the primary KS tissue; and 3) KS Y-1 cells induce angiogenesis, tumorigenesis, and metastatic disease in both beige nude XID and severe combined immunodeficient mice. Further, a high plating efficiency has been demonstrated, as well as the presence of telomerase (Gill PS: personal communication). Of interest, despite the identification of what appears to be a population of neoplastic KS cells, the precise origin of the KS cell remains a question, with the bulk of evidence supporting its origin from vascular endothelium. Of equal interest is the fact that no viral infections were identified within KS Y-1 cells. Employing specific antisera for viral proteins and polymerase chain reaction for viral nucleic acid sequences, all analyses were negative for HIV-1; cytomegalovirus; human herpesviruses (HHV) types 6, 7, and 8; human papillomavirus (HPV) type 16; HTLV I and II; herpes simplex viruses types 1 and 2; and hepatitis B and C viruses. The absence of viral sequences of HHV-8, the recently described so-called KS-associated herpesvirus (6), is particularly intriguing.

Using representational-difference analysis to identify unique DNA sequences associated with acquired immunodeficiency syndrome (AIDS)-related KS, Chang et al. (6) recently
demonstrated sequences of this newly identified HHV-8 in all 25 tissue specimens that were technically appropriate, but the sequences were largely absent in uninvolved tissues. This work has been confirmed by other investigators (7,8); the sequences have also been identified in tissues from classic KS (9,10) and from HIV-seronegative homosexual men with KS (10).

The absence of HHV-8 viral sequences in the neoplastic KS Y-1 line thus poses additional questions. It is certainly possible that HHV-8 is not the etiologic agent in KS, but serves as a passenger virus within these tissues. Alternatively, the virus may be etiologic and necessary for initial neoplastic transformation, with subsequent loss from involved tissues. In either case, the identification and propagation of the KS Y-1 cell line is expected to serve as an excellent model for KS, allowing more precise understanding of all the steps necessary in the development of neoplasia while also providing a model whereby potential new therapies may be tested. In fact, this latter role has already been confirmed by Lunardi-Iskandar et al. (11), who have demonstrated that the β chain of human chorionic gonadotropin induces apoptotic death in both KS Y-1 cells in vitro and KS Y-1-induced tumors in vivo, after inoculation into immunodeficient mice.

Aside from serving as models from which to explore the pathogenesis, treatment, and prevention of neoplastic disease, the report by Cleghorn et al. (1) and the article by Lunardi-Iskandar et al. (2) also serve to emphasize a new era in our understanding of many neoplastic disorders that are ultimately caused by viral organisms with oncogenic potential, manifested more easily and quickly, perhaps, in the setting of underlying immunodeficiency. Aside from HTLV-I-induced lymphomas and the possibility of HHV-8 as an etiologic factor in KS and in body-cavity-based, AIDS-related B-cell lymphomas (12), the Epstein-Barr virus has also been linked to numerous human tumors. These include malignant lymphomas in boys with the X-linked lymphoproliferative syndrome (13), high-grade B-cell lymphomas in HIV-1-infected patients with primary central nervous system lymphoma (14) and in some systemic lymphomas of immunoblastic or large cell type (15), lymphoproliferative disorders in patients who have undergone organ transplantation and subsequent iatrogenic immunosuppression (16), Hodgkin’s disease (in approximately 50% of cases, predominantly of the mixed cell type (17,18), smooth-muscle tumors in children infected with HIV-1 (19) and in patients who have undergone organ transplantation (20), and various T-cell lymphomas, including nasal T-cell lymphoma (21,22). Another DNA virus, HPV, has also been implicated in the pathogenesis of malignant disease in humans. Thus, HPV 16 and 18 have been linked to the development of anal cancer in homosexual men (23) and to cervical cancer in women (24). The role of immunosuppression in the full expression of HPV-induced neoplastic disease may be seen from recent data about women who have been coinfected with both HPV and HIV-1 (25). The incidence of such dual infection appears to increase with greater degrees of immunodeficiency (26), as does the prevalence of HPV-associated cervical intraepithelial neoplasia, which has been diagnosed in as many as 40%-50% of HIV-infected women at initial presentation (25-28). The designation of invasive cervical carcinoma as an AIDS-defining condition in January 1993 (29,30) lends further credence to the expectation that greater numbers of such cases will be diagnosed in the years ahead. It is apparent from these data that every attempt must be made to ascertain the precise steps necessary for the induction of human cancer by various DNA and RNA viruses. The work by Cleghorn, Lunardi-Iskandar, and their associates will provide new means by which such knowledge may be gained.

References

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T-Cell–Mediated Immunity to Carcinoembryonic Antigen in Humans: an Example of “Swimming Upstream”?

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In this issue of the Journal, Tsang, Schlom, and co-workers (1) demonstrate that a peptide from carcinoembryonic antigen (CEA) is capable of generating cytolytic T lymphocytes (CTL) in vitro from precursors present in cancer patients immunized with a recombinant vaccinia-CEA vaccine. The importance of this finding cannot be fully assessed until the theoretical value of vaccination with CEA has been determined. Yet, there is no doubt that the theoretical and practical significance of the results may well be profound.

First, the findings of Tsang, Schlom, and co-workers begin to demonstrate that CEA is immunogenic in humans, which was not intuitively obvious when their studies were begun. CEA was first described by Gold and Freedman (2), who thought that they had found the first tumor-specific antigen and emphasized its possible value in detecting early carcinomas of the colon. Unfortunately, both of these assertions proved to be incorrect. CEA had found the first tumor-specific antigen and emphasized its possible value in detecting early carcinomas of the colon. There should be more HTL-inducing epitopes than those sensitizing for cytotoxicity by CTL on the CEA molecule, judging from work with influenza viral proteins (3), but it has proved difficult thus far to demonstrate any HTL-inducing epitopes consistently in humans vaccinated with CEA [cf. reference 23 cited in (1)].

A fact that is largely lost in studies dealing with the demonstration of human tumor epitopes is that this feat has almost always required as reagents precursors of HTL and CTL.

REFERENCES


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