Immunological Control of Cervical Cancer: Discussion

Joseph L. Melnick

Department of Virology and Epidemiology, Baylor College of Medicine, Houston, Texas 77025

Neutralizing antibodies against herpesvirus type 2 are more frequently found in women with cervical cancer than in matched control women. This appears to be true not only for invasive carcinoma of the cervix but also for carcinoma in situ and cervical dysplasia. Since both cervical cancer and herpes type 2 infections are related to attributes associated with venerably transmitted agents, the association between the virus and the cancer could represent one of covariability. However, recent studies, including the comparison of cervical cancer patients with matched breast cancer patients of the same social group, support the hypothesis of a causal relation of the virus to cervical cancer. Also supporting the hypothesis are the recent findings of antibodies to herpesvirus-induced nonvirus antigens in cervical cancer patients, reviewed by 3 speakers at this meeting (1, 5, 8). The data are compatible with a model in which infection by the virus early in life leads to oncogenic changes that are expressed a number of years later.

In addition to the previously reported data on complement-fixing antibodies, new information is being obtained at Baylor, where a radioimmune assay has been developed to detect the presence in cervical cancer patients of antibodies that react with specific nonstructural polypeptides induced early in the HSV\(^2\) replicative cycle. Some cervical cancer patients were found with antibodies to early polypeptides but not to whole virus. Perhaps this test may be able to be executed more carefully and to whom existing preventive measures could be more intensively applied.

Studies of nucleic acid hybridization between HSV and cervical cancer were discussed by zur Hausen (13). Except for a single positive case (3), which is yet to be confirmed, all other attempts to find HSV-2 DNA in human tumors have failed. Moreover, there has not been success in finding HSV DNA in HSV-transformed rodent cells, even when assayed under conditions permitting the detection of 0.1 genome equivalent per cell. The HSV-transformed cell system is different in this regard from cells transformed by other herpesviruses (Epstein-Barr virus, Marek’s disease virus, and Herpesvirus saimiri). However, one should bear in mind that 0.1 of a HSV genome has a molecular weight of about 10 million daltons, and this amount would be much larger than the amount of DNA (1 million daltons) found in papovavirus-transformed cells.

A more sensitive approach seems to be to look for other evidence of genetic information in tumor cells. An example is the work by Kimura et al. (6, 7) at Baylor using temperature-sensitive mutants of HSV, which is discussed in my paper (8) in this Symposium.

One of the urgent problems that requires more attention is the usual failure to grow malignant cells from cultured human tumors. Tests for such malignant cells have utilized mice treated with antithymocyte serum or, more recently, nude mice. Another approach using an \textit{in vitro} marker of cancer is now being used by the Steiners in our laboratory, who have focused on the status of fucolipids in cultured malignant cells. A new series of 4 major radiolabeled fucolipids have been identified in a variety of normal cultured cells, including those from rat, hamster, mouse, baboon, and human tissue. Transformation of the animal cells by oncornavirus, herpes simplex virus, or simian virus 40 has resulted in a characteristic and marked decrease in the incorporation of radiolabeled fucose into the least chromatographically mobile, presumably most complex fucolipid. The observations in animal cells have recently been extended to a variety of cultured human tumor cells in which the decreased incorporation of radiolabeled fucose into the most complex fucolipid was also demonstrated. Hence, these results suggest the possible use of fucolipid metabolism as a diagnostic marker of \textit{in vitro} cancer in cultured human tumor material.

Research on model systems is encouraging, particularly the genital infection of female Cebus monkeys with HSV-2 and preliminary findings of animals with persisting anaplastic cervical cytology. Palmer et al. (10) reported on finding 8 monkeys with atypia and 5 with dysplasia in contrast to none in the controls in these studies that are still in prog-

---

1 Presented at the symposium "Immunological Control of Virus-associated Tumors in Man: Prospects and Problems," April 7 to 9, 1975, Bethesda, Md.

2 The abbreviations used are: HSV, herpes simplex virus; HSV-2, herpes simplex virus type 2.
ress. The laboratory evidence on the oncogenic potential of HSV is adequately summarized in this Symposium by Rapp and Reed (11).

Immunological aspects were reviewed by Nahmias et al. (9) (cell-mediated immunity) and by Hilleman (4) (humoral immunity). Successful herpesvirus vaccines of the live, attenuated variety have been developed for use in veterinary medicine, including one for controlling onco-nectic Marek's disease. However, because of the undesirable properties inherent in an attenuated live virus vaccine, particularly that of potential reversion to wild-type, latent infection, and even oncogenicity (Table 1), there is little to expect from such attenuated vaccines in the foreseeable future. In spite of this gloomy outlook, attenuated HSV mutants have been obtained, particularly by the selection of temperature-sensitive mutants as described in the paper from our laboratory (8) which appears in this Symposium. Studies on the nature of the immunity (e. g., to challenge virus or to challenge tumor cells) produced by attenuated HSV in rodents are now possible. These studies can even include primates if the attenuated HVS is used, for such an experimental attenuated virus vaccine has now been produced and shown to protect against lymphomas in marmosets (in cooperative experiments between Deinhardt's laboratory and our group).

It would seem that the most straightforward and safest approach to immunity at this time is through the use of inactivated or subunit vaccines. From the work to date, the use in humans of killed whole herpes simplex virions (as they exist in infected cell extracts) has not met with success. However, with another oncogenic herpesvirus, marmosets have been protected by heat-inactivated HVS from developing HVS-induced lymphomas. Hilleman (4) has reviewed the approaches to vaccination, and I would like to emphasize 3 points.

1. Regarding selection of strains for vaccine production, recent studies (12) indicate that strains of HSV-2 are not all antigenically identical. The results of 56Cr release assays, using antisera that had been adsorbed with virus-infected cells, demonstrated 2 subsets of HSV-2 strains; these subsets are called α and β. HSV-2 isolates were examined from different geographic areas. All 10 strains from Colombia, where significant differences in type 2 antibodies between cancer cases and controls were not found, belonged to Subset β, while 5 of 15 strains from the United States and 1 of 2 strains from India belonged to Subset α. The data suggested a correlation between virus subset and oncogenicity of HSV-2 in hamsters. Four of 5 α-viruses and 5 of 8 β-viruses transformed cells in culture, but only those 4 cell lines transformed by α-viruses were oncogenic when injected into hamsters. More work is required to assess the possible roles of α- and β-viruses in cervical cancer and for possible vaccine stocks.

2. In the search for a subunit vaccine for HSV-2, work is going forward on the immunological characterization of individually isolated HSV polypeptides. As I previously discussed (8), Courtney and Powell (2) are now able to obtain pure polypeptides in large quantity and to determine their functions. VP123, the major envelope glycoprotein, has been used to produce antiserum that exhibits type-specific neutralization when caused to react with infectious virus. These methods offer a great potential to produce pure polypeptides free of nucleic acid that can be used for raising protective antibodies in humans. Such preparations may well become the vaccines of the future.

3. As mentioned in the beginning of this discussion, in spite of many retrospective studies, the etiological role of HSV-2 in cervical cancer remains to be proven. The most direct and rewarding proof could come from vaccinating high-risk populations. If HSV-2 infections can be prevented by vaccine, or perhaps even limited as in the case with Marek's disease vaccine, then cervical cancer should disappear as a disease. The ultimate proof of causation rests upon controlling the disease by eliminating or limiting the expression of the etiological agent.

References


2. Courtney, R. J., and Powell, K. L. Immunological and Biochemical Characterization of Polypeptides Induced by Herpes Simplex Virus Types 1 and 2. Proceedings of the Symposium on Oncogenesis and Herpesviruses, in press.


Immunological Control of Cervical Cancer: Discussion

Joseph L. Melnick


Access the most recent version of this article at: http://cancerres.aacrjournals.org/content/36/2_Part_2/859.citation

Sign up to receive free email-alerts related to this article or journal.
To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.
To request permission to re-use all or part of this article, contact the AACR Publications Department at permissions@aacr.org.