The inclusion of breast cancer in this symposium on virus-associated tumors in man presupposes that human breast cancer is induced by a virus or is at least strongly associated with a virus. At the moment, there appear to be 2 lines of evidence for this. The first is simply an analogy to the extensively studied mouse mammary tumor system, where a virus has been directly demonstrated. Much of the data presented at this meeting has related to this model system, with the implicit expectation that some or all of the information will be relevant to human breast cancer. The other line of evidence is quite recent and involves the accumulating data indicating biochemical and immunological cross-reactions of human breast cancer with MTV or with Mason-Pfizer monkey virus, and the presence of B-type particles in human milk and at least 1 tissue culture line derived from human breast cancer.

There are several points that came up during this meeting that should be emphasized, particularly with regard to the possible implications for human disease. In the mouse tumor systems, several laboratories are finding some relationship between tumor-associated antigens and MTV-associated antigens (3, 12). Such observations need to be explored further. For example, what is the relationship between ML antigen and gp52 of MTV. Further, is the serologically defined ML antigen the same as the detected by assays of cell-mediated immunity? These questions should be answered by further purification of the antigens and studies of cross-reactivity. It will be of particular interest to determine whether the gp52 is the major transplantation antigen associated with MTV, i.e., whether immunization with this antigen can protect mice against mammary tumor growth (12). During the course of the discussion, it was pointed out that some of the extracts now used, e.g., 3 M KCl extracts of tumors, are quite crude and can contain a variety of proteins and antigens, some of which may not even be truly soluble (12, 13).

Hosts respond differently to viral antigens depending on whether, when, and how they have been exposed to the virus (3, 12). Different MTV’s (at least with different pathogenic spectra) may have antigenic differences. The dynamic state and rapid turnover of some of these antigens have been emphasized (13), and the actual amount of viral-related antigens in different mouse mammary tumors has been shown to be variable and having an inverse relationship with normal membrane antigens, especially D-end antigens of the major histocompatibility complex (12). The complexities of the immune response to mammary tumors also became apparent, indicating different effector mechanisms operative at different stages of the response (3), as well as complex interactions among effector cells and antibodies, antigen-antibody complexes, and free antigen (3, 10, 12).

Evidence for individual antigens on mouse mammary tumors, in both MTV-containing and -negative strains, was presented. The relative role of these antigens as compared to MTV-associated antigens, is not clear. The data of Simmons et al.3 indicate that they may be important for protection, whereas those of Heppner et al. (5) raised the possibility of an enhancing function. Further information will be important, since the strategies related to immunoprophylaxis or immunotherapy of tumors with common transplantation antigens would be quite different from those in which individual antigens were more important. Clearly, the central issue is what manipulations will affect the growth of spontaneous tumors, rather than that of transplanted tumors. The experience of Simmons et al.3 of effective treatment of a particular tumor line without an effect on subsequent spontaneous tumors is discouraging in this regard.

Another important issue, which was discussed at some length, is the role of natural immunity to MTV and to mammary cancer. Several laboratories are detecting cell-mediated immunity in normal mice to MTV-associated antigens (3, 12). Thus far, the main value of this has been to point to frequent horizontal transmission of MTV (3). It will be of interest further to determine the nature of the cells mediating these natural immune responses and the relationship between these cells and those induced by deliberate immunization. The prognostic as well as diagnostic value of the natural response needs to be characterized. Of particular practical importance will be to establish the in vivo role of this natural immunity in protection against tumor growth. Will hormonal factors or other factors that have been suggested to affect the level of reactivity have a parallel effect on tumor growth? Can natural effector cells transfer protection against tumor growth to mice that lack this reactivity?

Concerning possible therapeutic or prophylactic uses of the present knowledge derived from the mouse, it is apparent that we need (a) a more detailed analysis of the natural as well as induced immune responses to the virus and to the antigens displayed in the tumor or preneoplastic...
O. Stutman and R. B. Herberman

lesion (possibly including development of other animal models such as dog, cat, etc.) and (b) a better biochemical characterization of the relevant viral as well as tumor-associated antigens. From this type of knowledge we may generate a "product" which may be used as a prophylactic vaccine preventing virus infection or controlling the magnitude of such infection and/or as a specific adjuvant for therapy of the established tumor, preventing malignant transformation of premalignant lesions, tumor spread, or residual disease (12). This last aspect implies the production of an immunogen (viral component?) that may permit therapeutic as well as prognostic approaches i.e., preventing recurrence of tumors in other mammary pads, a common feature in the mouse. It is also apparent from these listings that there are no limits to our wishful thinking and that, even in the well-studied experimental models, it seems difficult still to define the relevant antigens or the relevant immune responses that will permit a rational strategy for immunological prevention or control of virus-induced breast cancer.

The relevance of the mouse mammary tumor system to human disease would clearly be strengthened by evidence for a significant immunological cross-reaction between these diseases. Several intriguing pieces of data were presented on this but none are yet conclusive. Bowen et al. (4) showed that some sera from breast cancer patients react with MTV, even after absorption with normal mouse tissues or C57BL milk. However, some reactions have been eliminated by absorption with heterophile antigens and the possibility of some remaining reactivity with non-virus materials has not been excluded (4). The work of Newgard et al. (8) emphasized this reservation, showing that reactivity of human sera with MTV could be inhibited by dog milk. It was pointed out, however, that the significance of this is unclear, since large amounts of some materials can nonspecifically inhibit radioimmunoassays, with curves similar to those produced by specific antigens (8). In addition, the dog has a high incidence of breast cancer and the inhibitory activity may be an important clue to a homology to human and mouse breast cancer, rather than an artifact. A stronger immunological association between mouse and human breast cancer made by cell-mediated immunity data. The original observation of Black et al. (1, 2) of high frequency of reactivity in leukocyte migration inhibition assays of breast cancer patients to MTV-containing materials has now been confirmed (7, 10). In addition, similar data have been obtained in lymphocyte stimulation assays (Ref. 7; S. Cunningham-Rundles, personal communication). Further, Hollinshead et al. (6) have found that partially purified skin reactive antigens prepared from human breast cancer react with heterologous antisera against MTV or against Mason-Pfizer virus. Although these data are exciting, they must be viewed cautiously. The virus-containing preparations used to date have not been purified and may contain a number of non-virus-related materials, which could be responsible for the cross-reactions.

An obvious question to be raised in such a meeting was: If the association between an animal virus and human breast cancer is a real one, how might this be exploited for prevention or therapy of the human disease? There was a clear reluctance on the part of the participants to enter into this type of projection. The best high-risk population mentioned for study was the sisters and daughters of women with the familial form of breast cancer. However, there was virtually no discussion of the feasibility and possible hazards of an MTV vaccine or tumor extracts for administration to such individuals. Some of the mouse experiments showed the complexities and risks of the therapeutic approach (12). Most of the discussants stressed the diagnostic implications of virus-associated antigens or of immune reactivity to these antigens. Clearly, the development of practical assays that could distinguish between tumor-bearing or cancer-prone individuals and normal individuals could be very useful in screening. Much remains to be done to determine the feasibility of even this diagnostic approach.

References

Immunological Control of Breast Cancer: Discussion

Osias Stutman and Ronald B. Herberman


Updated version

Access the most recent version of this article at:
http://cancerres.aacrjournals.org/content/36/2_Part_2/781.citation

E-mail alerts

Sign up to receive free email-alerts related to this article or journal.

Reprints and Subscriptions

To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

Permissions

To request permission to re-use all or part of this article, contact the AACR Publications Department at permissions@aacr.org.