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Meeting Report

Sapporo Cancer Seminar: Escape of Tumor Cells from Immune Controls[1]

Most tumors in animals, and probably also in humans, grow progressively. This depressing fact has led many researchers to discount the view that the adaptive immune system of the host plays a role in the control of malignant cells. It may be argued, however, that immunosurveillance really exists, involving not only specific antitumor responses mediated by T-lymphocytes and/or antibodies but also a "natural resistance" involving macrophages and NK[2] cells. However, tumors may "escape" from host controls through a number of pathways. Understanding of these events will certainly be required if rational approaches to immunological control of cancer are to gain credence.

At one extreme, cells transformed by ubiquitous oncogenic viruses in mice, monkeys, and humans normally meet a virtually watertight immunosurveillance that effectively prevents their growth and development (G. Klein, Stockholm, Sweden). This phenomenon is not directed against the virus but against virally induced membrane components on the transformed cell. Escape from multieffector controls may then occur in various ways, including breakdown of host control as in chronic mononucleosis, X-linked lymphoproliferative syndrome, and renal transplant lymphomas. This process is clearly distinct from escape due to cytogenetic change as typified by Burkitt's lymphoma (G. Klein).

The opposite extreme is exemplified by UV-induced murine squamous cell carcinomas which are highly immunogenic but are prevented from being rejected by the impairment of several immunological responses, particularly through the generation of suppressor T-cells (M. Kripke, National Cancer Institute, Frederick, Md.). These are examples of normally good host recognition, but antitumor responses are suppressed. In these cases, the induction of suppressor T-cells arises as a consequence of UV irradiation, possibly at the level of cells involved in the uptake, processing, and presentation of tumor antigen (M. Kripke). This UV effect perhaps mimics alternative pathways of recognition of tumor-associated antigen when presented in free form or as cell surface-expressed molecules. This view is expressed in numerous studies showing that shedding of tumor antigen into the circulation system occurs as an early response to tumor growth (R. Baldwin, Nottingham, United Kingdom). Different antigenic determinants may be responsible, however, for the generation of "cytotoxic" and suppressor T-cells (S. Fujimoto, Japan; D. Naor, Jerusalem, Israel). Experiments with the Moloney virus-induced YAC tumor show that soluble membrane products (M, $< 70,000$) induced antitumor T-cells whereas larger products (M, $> 100,000$) induced suppressor cells (D. Naor).

While there is still limited understanding of tumor antigen recognition, the generation of T-suppressor cells is an important pathway to escape from host controls. Presentations (T. Tachibana, Sendai, H. Kobayashi, Sapporo, Japan) that emphasized elimination of suppressor cell precursors by lymphocytotoxic chemotherapy enhances tumor immune response. Suppressor T-cells influence a number of antitumor responses including the generation of sensitized T-cells which are cytotoxic for tumor cells and/or function as accessory cells promoting the infiltration of activated macrophages and NK cells into tumor deposits.

Even when tumors can be shown to have tumor antigens, for example by the induction of tumor immunity in normal hosts, are they adequately expressed in a growing tumor? This expression will influence the capacity of the antigen both to elicit antitumor responses in the tumor-bearing host and to serve as receptors on tumor cells for sensitized T-cells or antibody. Modulation of target cell susceptibiity to cytotoxic T-cells has been observed with murine tumors (EL4, P815Y) so that tumors beyond a critical mass become resistant (J. Palmer, Philadelphia, Pa.). Also, tumor-specific antigen associated with rat mammary carcinoma was revealed upon cells derived from solid or ascitic tumor growths only after mild trypsin treatment (R. Baldwin). This observation suggests that modulation and/or masking of antigen on tumor cells *in vivo* represents another pathway of escape (progression), leading eventually to selection of tumor cell populations with reduced immunogenicity and increased tumorigenicity (H. Ioachim, New York, N. Y.).

Escape defined in terms of loss of tumor antigen recognition may be a more basic phenomenon, perhaps related to tumor progression. This is evidenced by the identification of tumor cell populations with varying sensitivities to antibody-complement-mediated killing (S. Ohanian, Bethesda, Md.). This sensitivity appears to be principally related to the ability of cells to repair potentially cytotoxic damage and not to cell surface properties such as membrane fluidity. The observation that chemotherapeutic agents restore sensitivity to C-mediated attack again emphasizes the still largely unexplored potential of combination therapy (E. Mihich, Buffalo, N. Y.).

Tumor cell modulation is also of considerable importance in allowing esape of tumors to form metastases. The isolation of subclones from murine tumors with enhanced capacity for lung colony formation and an associated genetic instability (as determined by spontaneous mutation rate) may be viewed as one example of a tumor progressing toward a more stable state (I. Fidler, National Cancer Institute, Frederick, Md.). The concept that suppression of host recognition allows metastatic spread of tumors is more contentious. With immunogenic tumors, suppression of T-cell response leads to enhanced metastatic spread which can be affected experimentally by immunosuppressing the host or by inducing tolerance to tumor-associated antigens (T. Hamaoka, Osaka, Japan). Variability in NK cell sensitivity may also play a role in metastasis. For example, tumor cells freshly isolated from lung and lymph node metastases of spontaneous rat mammary carcinomas show markedly reduced sensitivity to lysis by NK cells. This altered sensitivity

[1] Report of the First Sapporo Cancer Seminar, held in Sapporo, Japan, July 15 to 18, 1981. The chairman of the meeting was Professor H. Kobayashi (Sapporo).

[2] The abbreviation used is: NK, natural killer.

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is frequently due to changes in the intrinsic lysability of the tumor cells rather than to altered expression of the NK target structure (G. Flannery, Nottingham, United Kingdom). In contrast, both primary and metastatic murine tumors are susceptible to destruction by activated macrophages. This property has led to the development of novel immunotherapeutic manipulations in which macrophage-activating agents such as muramyl dipeptide are encapsulated in liposomes designed to localize at appropriate tissue sites such as the lung (I. Fidler).

Undoubtedly, the most effective mechanism for a tumor to escape from host recognition is not to be identified. Many naturally arising (spontaneous) tumors fall into this category. However, these tumors, arising through a process of multistage progression, may already have been selected (modulated) for nonrecognition. It is not true, however, that all spontaneous tumors lack immunogenicity since some can induce tumor rejection responses when transplanted into syngeneic recipients (R. Baldwin).

By treatment of tumor cells with potent mutagens, it is possible to obtain with high-frequency stable tumor cell variants that are immunogenic (T. Boon, Brussels, Belgium). Applying this technique to a "nonimmunogenic" murine thymic leukemia yields variants conferring protection against the original tumor line. These variants arise with a frequency much greater than that expected by mutagenicity, so the mutagen treatment may reverse a process of tumor antigen modulation. This concept would be in accord with the conclusions of other presentations on tumor dormancy, immunoselection, and immunomodulation in suggesting that, under certain conditions, tumor antigens become "silent." Immunomodulation was demonstrated, for example, with the EL4 and P815Y tumors in mice where cells derived from lesions beyond a critical size showed resistance to cytotoxic T-cells due to a reduction in expression of tumor antigen (J. Palmer). In other studies with L5178Y lymphoma, a tumor "dormant state" was established in which the proliferating fraction of a tumor was destroyed by cytolytic T-cells without completely eliminating the tumor, presumably because of loss of recognition (E. Wheelock, Philadelphia, Pa.).

These considerations lead to the premise that it should be possible, at least with certain tumors, to restore or enhance immunogenicity. As already indicated, restoration has been achieved following treatment of murine tumors with mutagens (T, Boon). Adaptive immune responses may also be enhanced by viral xenogenization of tumors; Kobayashi showed that "modified" tumor cells produced strong immunity against the original tumor. Rescue of the murine sarcoma virus genome in a murine sarcoma virus-induced rat embryonal carcinoma which normally did not produce C-type virions, rendered this tumor highly immunogenic. However, the rescue did not induce any immunity to the original tumor, which was essentially nonimmunogenic. These studies suggest that virus-associated antigens induced in xenogenized cells function as helper determinants, enhancing tumor immune responses rather than reexpressing silent antigens. This concept is compatible with experiments showing that tumor cells coupled to tuberculin protein to promote T-helper cell responses were highly effective for inducing tumor immunity (T, Hamaoka).

Several contributors argued that circumventing these effects may be a more general approach in promoting host resistance. Treatment with cytotoxic drugs may eliminate suppressor T-cells so stimulating host response to tumors (E. Mihich). One response following interaction of sensitized T-cells with tumor cells is the generation of factors increasing the infiltration of macrophages and NK cells into tumors. Indeed, in many cases, these factors may be the effectors mediating tumor cell killing rather than cytotoxic T-cells. Therefore, control of effector: suppressor T-cell population will be important in promoting antitumor responses. These responses emphasize that circulating factors, including tumor antigens and immune complexes, originally described as blocking factors, may influence the capacity of sensitized effector cells to extravasate into tumor deposits.

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