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Commentary

Inducing autoimmune disease to treat cancer

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For many years, visions for development of successful immunotherapy of cancer revolved around the induction of immune responses against tumor-specific "neoantigens." However, as demonstrated in a recent paper in the *Proceedings* by Overwijk *et al.* (1), the generation of tissue-specific autoimmune responses represents an approach to cancer immunotherapy that is gaining momentum. Thus, a new principle in cancer therapy states that the ability to induce tissue-specific autoimmunity will allow for the treatment of many important cancers.

The original focus on tumor-specific neoantigens derived from a number of findings. Vaccination-challenge experiments performed between carcinogen-induced murine tumor models typically demonstrated that autologous tumors vaccinated much more effectively against themselves than against other independently derived tumors even of the same histologic type (2). These results were taken to imply that unique antigens specific to a particular tumor were more "immunogenic" than shared antigens that would be expressed by multiple different tumors. This implication appeared to be corroborated when T cell clones raised against murine tumors were found to be specific exclusively for the tumor against which they were raised and failed to recognize other tumors derived from syngeneic animals (3). The revolution in cancer genetics provided an apparent molecular basis for these experimental findings. As it became clear that cancer was a disease characterized by genetic instability (4), the tremendous array of genetic alterations unique to each tumor could provide unique peptide sequences, which when presented on a tumor's MHC molecules would represent tumor-specific neoantigens capable of being recognized by T cells. Such a view of the tumor-specific antigen was quite distinct from the majority of tumor antigens recognized by antibodies, which tended to recognize ubiquitously expressed cell-surface antigens whose structure was modified in tumors by posttranslational events, most commonly altered glycosylation (5).

From the standpoint of immunotherapy, the concept of targeting unique tumor-specific antigens provided two fundamental advantages. First, immune responses targeted against unique antigens theoretically would be exquisitely tumor-specific and produce no collateral damage to normal cells. Second, it was imagined that immune tolerance to tumor-specific neoantigens might not be particularly stringent as these would have arisen subsequent to development of the mature adult immune system. Thus, tolerance to neoantigens could be broken or superceded more easily than tolerance to self-antigens. These potential advantages are balanced against a significant disadvantage, namely that immune therapies targeted against unique tumor-specific antigens would by necessity be individualized rather than generic, thereby dramatically increasing the cost and labor intensity of treating large numbers of patients.

Over the past 5 years, a set of surprising experimental findings from studies of human antitumor immune responses has led to a shift in emphasis from unique tumor-specific antigens to tissue-specific self-antigens as promising targets for immune therapy. This shift began in 1994 when Coulie and colleagues (6) discovered that the target for a melanoma-specific $CD8^+$ T cell clone grown from a melanoma patient was wild-type tyrosinase, a melanosomal enzyme selectively expressed in melanocytes and responsible for one of the steps in melanin biosynthesis. Subsequently, a number of investigators found that their melanoma-specific $CD8^+$ T cells indeed recognized melanocyte-specific antigens rather than melanoma-specific antigens (7–10). Most of these antigens appear to be melanosomal proteins, and a number of them, including tyrosinase, TRP-1, TRP-2, and gp100, are involved in melanin biosynthesis. Other melanosomal proteins such as MART1/Melan A have no known function but are nonetheless melanocyte-specific tissue differentiation antigens. As the experience in identifying antigens recognized by melanoma-specific T cells expanded, it appeared that recognition of these melanocyte-specific differentiation antigens by melanoma-reactive $CD8^+$ T cells were not spurious events but rather represented the dominant target of immune responses. In contrast, recognition of peptides derived from unique tumor-specific mutations represented infrequent reactivities identified among melanoma-reactive $CD8^+$ T cells grown from melanoma patients (11–13). Regarding MHC, class II restricted CD4 responses, whereas the majority of these seemed to recognize unique antigens (in contrast to CD8 responses) responses against wild-type tyrosinase peptides were nonetheless identified from among panels of MHC class II-restricted $CD4^+$ melanoma reactive T cells (14, 15). Additional evidence for the relevance of tissue-specific antiself responses in melanoma immunotherapy came from the finding that patients whose tumors responded to IL-2-based immunotherapy occasionally developed vitiligo (autoimmune depigmentation of patches of skin), whereas vitiligo was essentially never seen among melanoma patients whose failed to respond to immunotherapy (16).

These findings generated both surprise and excitement among the cancer immunology and autoimmunity communities. They created an important scientific linkage between the cancer immunology and autoimmunity fields in that antitumor immune responses and autoimmune responses now could be viewed as opposite faces of the same coin (17). Stated more practically, given that so many of the common cancers are derived from dispensable tissues (e.g., melanoma, prostate cancer, pancreatic cancer, and breast cancer), induction of immune responses against tissue-specific antigens shared by these tumors might represent an immunotherapy approach whose autoimmune side effects would represent acceptable collateral damage. Thus, principles learned from the dissection of mechanisms by which tolerance is broken to cause autoimmune disease could be applied to the generation of cancer immunotherapy targeted toward tissue-specific autoantigens. Indeed, investigators have identified a number of important factors in the activation of autoimmune responses. Certain MHC types predispose to susceptibility to spontaneous as well as experimentally induced autoimmune disease, presumably the cause of their ability to present particular self-epitopes.

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One of the holy grails in the autoimmunity field is the identification of the initiating antigenic targets for autospecific responses. An underlying hypothesis in the field states that initiating autoantigens represent "cryptic" epitopes, which, because they are not normally presented at high density, do not induce active tolerance within the immune system (18). Induction of autoimmune responses is believed to occur when these cryptic epitopes somehow become presented at higher density and also are presented in the context of active immune responses induced by infection with a foreign pathogen (19). Thus, as the scenario goes, a susceptible individual is exposed to an infectious agent that expresses epitopes that mimic self-antigens. Inflammatory signals such as cytokines and other signals provided by T cells reacting to foreign epitopes on the virus lead to a cascade of responses that activate latent T cell responses against the self-antigen. If these latent T cell responses can become appropriately activated and sustained, they are capable of recognizing lower concentrations of the self-epitope on normal tissues and therefore can initiate an autoimmune reaction.

Recently, there have been an increasing number of examples of antigen or epitope mimicry between antigens on infectious organisms and self-antigens that are candidate targets for associated autoimmune diseases. One of the best examples with demonstrated physiologic relevance is the reported mimicry between an epitope from the spirochete causing Lyme disease and LFA-1, a candidate target for immune responses in Lyme-associated arthritis (20). An important feature of either spontaneous or experimentally induced autoimmune disease is that the ability to break tolerance and induce autoimmunity is highly dependent on the particular autoantigen. By analogy, it follows that attempts to induce autoimmune responses against tissue-specific self-antigens as a strategy for cancer immunotherapy would depend significantly on which antigen was chosen.

The experiments reported by Overwijk *et al.* (1) indeed represent a dramatic example of this principle. They set up an antigen mimicry version of cancer immunotherapy by producing a panel of recombinant vaccinia that incorporated the murine homologues of each of the defined melanocyte-specific differentiation antigens targeted by T cells from human melanoma patients and analyzed each of the recombinant vaccinia for their ability to induce vitiligo in C57BL6 mice as a measure of induction of tissue-specific autoimmunity. This finding was correlated with the different recombinant vaccines' ability to induce protection against challenge with the C57BL6-derived B16 melanoma. This system holds all variables (strain of mouse, immunization vector, and tumor challenge) constant while varying only the melanocyte-specific antigen incorporated into the vaccine. In so doing, they found that only recombinant vaccinia expressing TRP-1 induced vitiligo or protected against B16 melanoma challenge. These experiments add to the growing list of approaches that are inducing autoimmune disease and concomitant antitumor immunity. The study by Overwijk *et al.* represent the most clear-cut and dramatic demonstration of the importance of the particular antigen in the ability to break tolerance and cause autoimmunity and a therapeutic antitumor response.

A number of additional interesting findings fall out of these experiments. One of the most important outcomes is the lack of correlation between induction of $CD8^+$ cytotoxic T lymphocyte (CTL) specificity and autoimmunity or antitumor immunity. Indeed, the dominant melanocyte-specific antigen recognized by B16 reactive CD8 T cells is not TRP-1, but rather, TRP-2 (21). CTL against a second melanocyte antigen, gp100, could be elicited by immunization of mice with human gp100, which fortuitously generates a heteroclitic response against the corresponding murine gp100 epitope (22). However, neither vaccinia-TRP-2 nor vaccinia-gp100 immunization induced any vitiligo or antitumor immunity. Furthermore, the ability to induce vitiligo and antitumor immunity by vaccinia-TRP-1 relied not on the presence of CD8 cells but rather on CD4 T cell responses. This finding, together with recent experimental data demonstrating the central role of $CD4^+$ T cell responses and antitumor immunity (23–28) should help to cure the cancer immunology field of its tunnel-vision obsession with $CD8^+$ CTL as the only relevant immunologic antitumor effector. These findings also correlate with the general principle that MHC-linked susceptibility to autoimmune disease usually maps to MHC class II rather than MHC class I loci.

A final point worth considering in the discussion of harnessing autoimmunity for cancer therapy relates to the relative importance of the antigen chosen for vaccination versus the adjuvant or vehicle for antigen delivery during the immunization. In the Overwijk *et al.* studies (1), the immunologic "adjuvant" was the vaccinia virus in which the TRP-1 gene was incorporated. Recombinant viral vectors represent one of an ever increasing array of approaches to create inflammatory or "danger" responses that will enhance the activation of a cryptic T cell repertoire specific for these antigens (29). To determine the relative importance of antigen vs. adjuvant, one would need to hold the antigen constant and instead vary the adjuvant or vaccine vector used to initiate the immunization.

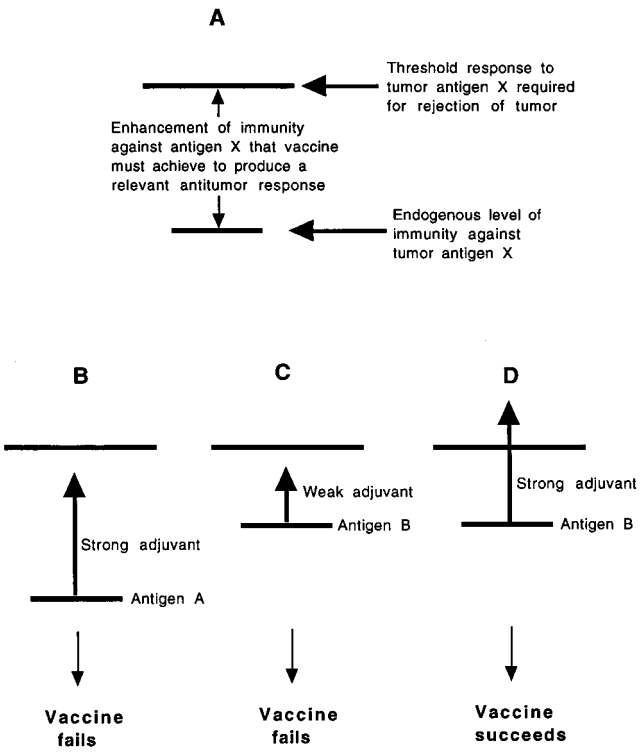

FIG. 1. Depiction of tumor antigen immunity as a potential energy diagram. Under normal circumstances, the level of endogenous immunity against a tumor antigen is below a critical threshold necessary for clinical antitumor immunity. Generation of an antitumor response would require the elevation of immunity against a particular antigen above a critical threshold. The stringency of tolerance against a particular antigen is represented by the "distance" of the endogenous immunity level below the reactivity threshold level (*A*). If one chooses an antigen against which immune tolerance is stringently maintained, even a strong adjuvant will not raise the level of immunity above the critical threshold and the vaccine will fail (*B*). If one chooses an antigen against which immune tolerance is less stringently maintained but uses a weak adjuvant, the vaccine also will fail (*C*). However, if one uses a strong adjuvant to present an antigen against which endogenous tolerance is relatively nonstringent, then it will be easier to elevate the level of immunity against that antigen above the critical threshold and the vaccine will succeed (*D*).

It is likely that both the specific antigen as well as the form of immunologic adjuvant will be critical in defining the qualitative and quantitative nature of immune responses generated. One might imagine a scenario depicted schematically in Fig. 1 in which the level of immunity against a particular tumor or self-antigen is viewed as a potential energy diagram. Under normal circumstances, the level of endogenous immunity against this antigen is below a critical threshold necessary for clinical autoimmunity or antitumor immunity. A successful autoimmune or antitumor response would require the elevation of immunity against a particular antigen above a critical threshold. The stringency of tolerance against a particular antigen is represented by the "distance" of the endogenous immunity level below the reactivity threshold level. If one chooses an antigen against which immune tolerance is maintained relatively nonstringently (such as TRP-1 in the Overwijk experiments), then it will be easier to elevate the level of immunity against that antigen above the critical threshold. In such a model, the correct choice of both antigen and adjuvant is critical. Furthermore, synergistic approaches to interfere with immunologic checkpoints that down-regulate immune responses (such as blocking CTLA-4 or FASL-FAS interactions) might further enhance the elevation of antitumor immunity (30, 31). The next decade will indeed see an increasing number of attempts to harness autoimmunity as therapy against cancer.

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