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Shedding Light on Immunotherapy for Cancer

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The realization that human cancers express cancer-associated antigens has stimulated research into the development of immunotherapies to mediate the regression of established tumors. There are three requirements for an effective immunotherapy for cancer (Fig. 1). A sufficient number of avid tumor-reactive lymphocytes must be present in the tumor-bearing host, these lymphocytes must be capable of reaching and extravasating at the site of the cancer, and the lymphocytes at the tumor site must have appropriate effector mechanisms to destroy cancer cells.

A recent study goes some way toward understanding the second requirement. Yu et al.¹ show that inserting a gene encoding a member of the tumor necrosis factor superfamily, referred to as TNFSF-14, or LIGHT, into a mouse tumor-cell line that was engineered to express an alloantigen (called H-2^d) prevents the cell line from establishing a tumor when it is injected into mice. LIGHT acts as a tether between the tumor stroma and T lymphocytes; it binds receptors on each. Stimulation of the stromal receptor triggers the up-regulation of molecules that help to attract T lymphocytes, thus increasing the infiltration of lymphocytes into the growing tumor that expresses LIGHT and priming these lymphocytes to react against and destroy the tumor. Preliminary experiments suggest that distant tumors might be affected as well.

A variety of problems, however, have plagued the translation of results obtained in animal models into effective immune-based treatments of cancer in humans; the study by Yu et al.¹ is not exempt from these problems. The authors focus mainly on immunization strategies that can prevent the establishment and outgrowth of a transplanted tumor, but effecting the regression of established, invasive, vascularized cancers is more difficult, since the three requirements must be met and there are currently no immunization strategies capable of meeting them. And although the genetic tweak engineered by Yu et al.¹ is sufficient to trigger an effective host response to a tumor bearing the H-2^d alloantigen, this strong antigen is an unrealistic surrogate for human cancer antigens. Most human cancer antigens are normal, nonmutated differentiation molecules or nonmutated proteins found only in tumor or germ cells; the human immune system seems to be more tolerant of these antigens than the mouse system is of alloantigen.

No experiments in mouse models have demonstrated that immunization against cancer (through the use of cancer vaccines) can reproducibly result in the destruction of large, well-vascularized mouse tumors expressing natural, nonmutated antigens. It therefore comes as no surprise that efforts to develop therapeutic cancer vaccines in humans have been unsuccessful thus far. Although large numbers of circulating T lymphocytes capable of recognizing cancer antigens can be induced in patients with cancer, especially by immunization with peptides emulsified in immune adjuvants, only rare and sporadic regressions of established tumors that meet rigorous oncologic criteria for a clinical response have been reported.²

The lack of clinical responses points to the need to overcome the escape mechanisms of tumors. The inability of immune lymphocytes to home to and infiltrate tumor tissues, as discussed by Yu et al., is one of several obstacles raised by the tumor to prevent its destruction. Other escape mechanisms include the loss of antigen expression by the tumor, the local presence of

immunosuppressive factors or cells, and the inability of the tumor to activate anti-tumor precursors. T lymphocytes that are generated by vaccines may not be numerous or avid enough, or they may be “tolerized” or “anergic” and thus unable to interact appropriately with the tumor.³

Although current approaches involving cancer vaccines have not yet been successful in patients, the alternative approach of cell-transfer — cancer therapy, based on the ability to sensitize and expand, ex vivo, autologous lymphocytes with the ability to recognize, reach, and destroy cancer cells — can overcome some obstacles to the development of effective cancer treatment (Fig. 1). The advantages of this approach include the ability to administer very large numbers of highly selected cells with high avidity for tumor antigens and the ability to generate and activate the cells ex vivo (away from suppressive influences in the host), so that they have appropriate antitumor effector functions and reach the tumor site. Especially important is the ability to manipulate the host before the autologous cells are transferred — for example, by eliminating host lymphocytes, including regulatory T cells — thus providing the transferred antitumor lymphocytes with an optimal environment.

The use of this approach in animal models has established principles that have clinical application,⁴ and in a recent study, this approach resulted in the regression of metastatic melanoma refractory to standard treatment in 46 percent of patients.⁵ The study by Yu et al.¹ suggests that the use of additional measures, which can increase the access of T lymphocytes to tumor, may increase the proportion of patients with a positive outcome.

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Figure 1. Two Approaches to Immunotherapy

The two main approaches to immunotherapy for cancer are vaccine therapy and cell-transfer therapy. Three steps are required for effective treatment: there must be sufficient numbers of lymphocytes with avid recognition of tumor antigens; these lymphocytes must reach the tumor; and once there, they must be able to destroy the tumor cells. Cancer vaccines depend on the in vivo generation of immune cells by an immunizing vector. Yu et al.¹ used an approach that increases the exposure of T lymphocytes to tumor tissue; they immunized mice with cells modified to secrete a molecule that enhances the flow of naive lymphocytes into tumor tissue and, hence, their sensitization to tumor antigen. Cell-transfer therapies involve sensitizing autologous lymphocytes ex vivo, expanding the population, and then infusing the lymphocytes into the host.