

REVIEW ARTICLE

MOLECULAR ORIGINS OF CANCER

Cancer Immunology

Olivera J. Finn, Ph.D.

From the University of Pittsburgh School of Medicine, Pittsburgh. Address reprint requests to Dr. Finn at the Department of Immunology, University of Pittsburgh School of Medicine, E1044, Biomedical Science Tower, Pittsburgh, PA 15261, or at ojfinn@pitt.edu.

N Engl J Med 2008;358:2704-15.

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MAJOR CONCEPTUAL AND TECHNICAL ADVANCES IN IMMUNOLOGY OVER the past 25 years have led to a new understanding of cellular and molecular interplays between the immune system and a tumor. This review deals with important new concepts in antitumor immunity and their application to immunotherapy.

TUMOR ANTIGENS

IDENTIFICATION

The immune system can respond to cancer cells in two ways: by reacting against tumor-specific antigens (molecules that are unique to cancer cells) or against tumor-associated antigens (molecules that are expressed differently by cancer cells and normal cells).¹ Immunity to carcinogen-induced tumors in mice is directed against the products of unique mutations of normal cellular genes. These mutant proteins are tumor-specific antigens.² Tumors caused by viruses display viral antigens that serve as tumor antigens. Examples are the products of the *E6* and *E7* genes of the human papillomavirus, the causative agent of cervical carcinoma,³ and EBNA-1, the Epstein-Barr virus nuclear antigen expressed by Burkitt's lymphoma and nasopharyngeal-carcinoma cells.⁴

Whether tumors of unknown cause — which account for most human tumors — express antigens that the immune system can recognize remained in doubt until the development of methods for detecting and isolating them. The advent of hybridoma technology⁵ led to the development of monoclonal antibodies from mice that were immunized with human tumors. Monoclonal antibodies that reacted specifically with tumor cells were then used to characterize putative human tumor antigens.⁶ Nevertheless, there were doubts that the tumor-specific antigens that mouse monoclonal antibodies could detect would be recognized by the human immune system.

The development of methods to propagate human T cells,⁷ and in particular tumor-specific T cells from patients with cancer, led to an important breakthrough: the identification of MAGE-1, a melanoma-specific antigen that stimulates human T cells in vitro. With antigen-specific T cells as a reagent, it was possible to clone the *MAGE-1* gene.⁸ The MAGE-1 studies showed that the human immune system can respond to tumor antigens, and the findings stimulated a productive effort to discover tumor antigens. The result is a long and still-growing list of antigens from a variety of tumors that could serve as targets for treatment.^{1,9}

The proteasomes of normal and neoplastic cells break down proteins into short peptides, and major-histocompatibility-complex (MHC) class I molecules on antigen-presenting cells present these peptides to cytotoxic CD8 T cells. Peptides derived from products of mutated genes or abnormally expressed cancer-cell proteins can also be presented to T cells (Fig. 1).¹⁰ Peptides bound to MHC class I or MHC class II

molecules of tumors have been sequenced in a search for tumor-specific antigens.¹¹⁻¹³ The ability to propagate dendritic cells¹⁴ made it possible to reconstitute an immune response in vitro. Dendritic cells could be loaded with various tumor-derived peptides, proteins, or even whole tumor cells and cultured with T cells, mimicking what occurs in vivo (Fig. 2). Peptides of interest were identified by their ability to expand a population of tumor-specific T cells in vitro.¹⁵ These efforts identified more than 100 peptides; some were derived from proteins that were products of unique mutations, but most were derived from normal proteins that were differentially expressed by tumor cells.

Peptides from cyclin B1 are tumor antigens that were discovered in this way. The cyclin B1 antigen was found by a method that entailed elution of peptides from MHC class I antigens on tumor cells, loading of these peptides onto dendritic cells, culture of the dendritic cells with T cells, expansion of tumor-specific T cells in vitro, and sequencing of the peptides that stimulated the T cells. This process yielded four peptides with sequences that indicated their derivation from cyclin B1.¹⁶ Cyclin B1 is barely detectable in the nucleus of normal dividing cells during the transition from the G2 to the M phase of the cell cycle. In many human tumors, by contrast, cyclin B1 is constitutively overexpressed in the cytoplasm. The immune system of patients with tumors that contain such abnormally expressed cyclin B1 can recognize the cyclin B1 antigen.¹⁷

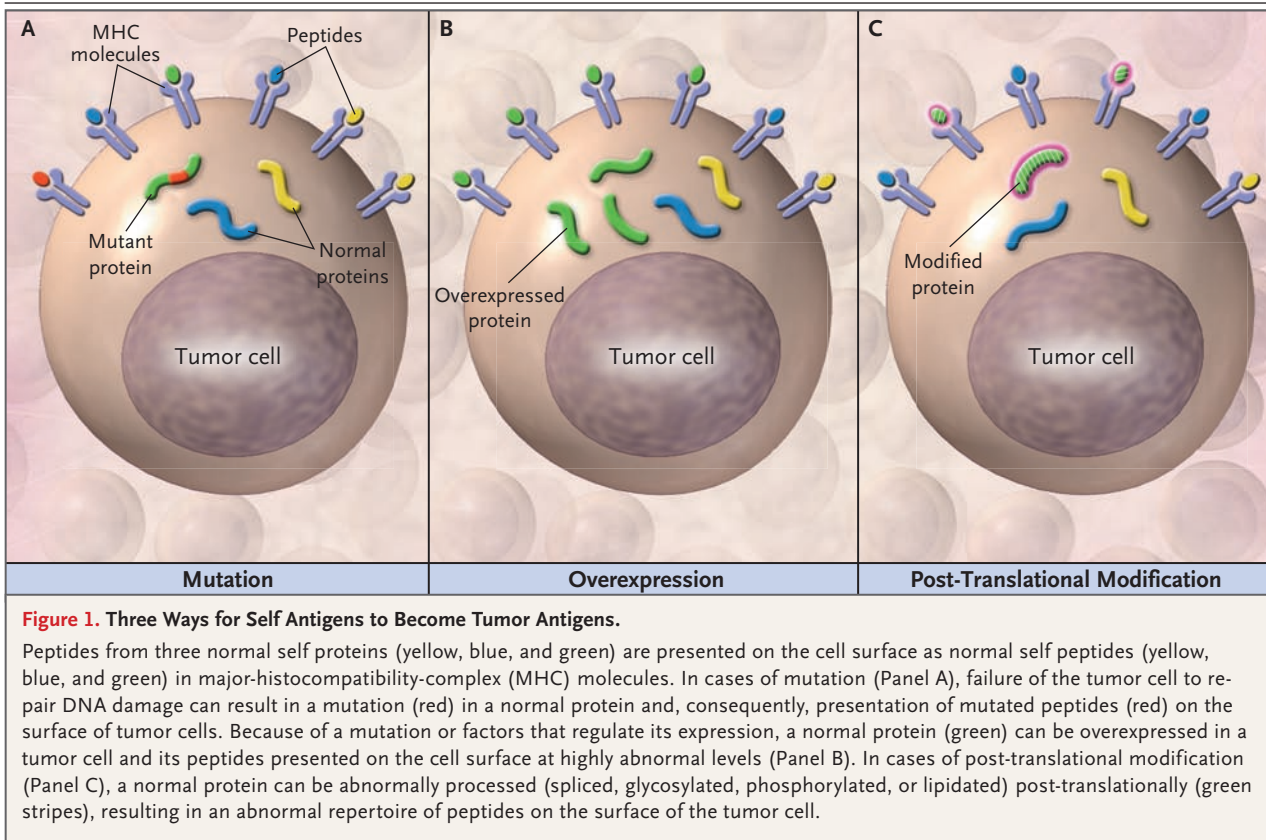
Another approach to the identification of tumor antigens involves analysis of serum samples from patients with particular neoplasms for immune reactivity with proteins extracted from tumor cells or made by complementary DNA expression libraries of tumors.¹⁸ Proteins recognized by antibodies in serum samples from patients with a particular tumor, and not from healthy controls, were tagged as candidate tumor antigens. One of the most actively studied tumor antigens, NY-ESO-1, was discovered this way.¹⁹ This molecule belongs to a family of cancer-testis antigens that are expressed by a variety of human tumors but not by any normal cells or tissues, except for the testis. The melanoma antigen MAGE-1 belongs to the category of cancer-testis antigens.

With so many tumor antigens, it is important to establish criteria for selecting particular ones for clinical development. Safety is of paramount

concern, especially in the case of aberrantly expressed autoantigens. As a first criterion, it is essential to ensure that immune responses against tumor antigens can destroy tumor cells but not normal cells. Preclinical testing of vaccines based on tumor-associated antigens CEA,²⁰ MUC1,²¹ and Her2/*neu*²² in mice that are engineered to express normal forms of these molecules has shown tumor rejection without any autoimmunity. Nevertheless, clinical trials will be the ultimate test of the safety of such vaccines. The second criterion is the status of the antigen in the tumor; an immune response against a tumor-specific antigen would be irrelevant if a tumor cell mutated in such a way that it no longer expressed the antigen in question and thereby avoided destruction by the immune system. Broad applicability of a vaccine against all tumors of a particular type or against many types of tumors is another important criterion, with a preference for shared antigens over antigens resulting from unique mutations.

IMMUNOGENICITY

It was once assumed that even if a cancer cell expressed tumor antigens, the tumor could not support immune activation because it could not induce inflammation (since a tumor is not a pathogen). This assumption has not been validated by recent studies, however. Products of oncogenes that become activated early in the development of tumors can incite strong inflammatory responses. For instance, lung tumors in mice that are initiated by a mutation in the *K-ras* oncogene produce chemokines that summon immune cells to the microenvironment of the tumor,²³ and the RET-PTC protein, the product of two fused oncogenes that drives the development of thyroid cancer, modulates nuclear factor- κ B, a transcription factor that controls the production of immunoregulatory cytokines. The RET-PTC protein increases production of granulocyte-macrophage colony-stimulating factor (GM-CSF) and monocyte chemoattractant protein 1, thereby creating a proinflammatory microenvironment.²⁴ Products of dying tumor cells (e.g., heat-shock proteins and monosodium urate) are some of the many inflammatory substances in the tumor microenvironment that are danger signals to the immune system.²⁵ Furthermore, the tumor antigens MUC1,^{26,27} CEA,²⁸ and NY-ESO-1²⁹ have been shown to attract innate inflammatory responses, and thus can also be considered to be danger signals.



IMMUNOSURVEILLANCE OF CANCER

The immunosurveillance hypothesis posits that the immune system recognizes malignant cells as foreign agents and eliminates them. This idea was contentious until our understanding of tumor immunity improved and better techniques and animal models became available to test it rigorously. Mouse models in which immune effector mechanisms such as the type 1 interferons were eliminated by gene deletion showed a clear reduction in the incidence of tumors by the immune system.³⁰⁻³⁴ In animal models, the encounter between the immune system and a nascent tumor initiates a process termed “immunoediting”³⁵ that can bring about three outcomes: elimination of the cancer; cancer equilibrium, in which there is immune selection of less immunogenic tumors during an antitumor immune response³⁶; and tumor escape, the growth of tumor variants that resist immune destruction.³⁵

Experimental evidence of immunosurveillance in humans is difficult to obtain because of the requirements for large numbers of subjects and

long-term follow-up. Nevertheless, investigations to determine whether immune function is associated with the incidence of cancer have implicated both innate and adaptive immunity. A recent study examined 905 recipients of transplanted hearts, lungs, or both between 1989 and 2004 for the effect that immunosuppression, used for preventing graft rejection, had on the incidence of cancer.³⁷ A total of 102 newly diagnosed cancers were detected in these patients, which is 7.1 times as many as in the general population. The predominant types were leukemias and lymphomas (26.2 times as many as in the general population), head and neck cancer (21 times as many) and lung cancer (9.3 times as many). Nonmelanoma skin cancers were not considered in this count. Another study, an 11-year follow-up of 3625 healthy people in Japan, showed that the subjects whose blood lymphocytes at the beginning of the study had a high or medium degree of natural cytotoxicity had a significantly lower risk of cancer of any type than did subjects whose lymphocytes had a low degree of cytotoxicity.³⁸

The immune system also influences the recur-

rence of cancer. A recent study of three multicenter cohorts of 603 patients with colon cancer showed that the presence or absence of T cells in the resected tumor predicted the clinical outcome more accurately than tumor stage and nodal status, the current gold standards.³⁹ Similar observations have been made in tumor specimens from patients with cervical cancer,⁴⁰ breast cancer,⁴¹ urothelial carcinoma,⁴² and follicular lymphoma, as well as in lymph nodes draining the tumor site.^{43,44} All these studies led to the conclusion that an evaluation of the immune response in and around the tumor should be included in the prognostic evaluation and in treatment decisions.

IMMUNOSUPPRESSION AND TUMOR PROGRESSION

Tumors can suppress immunity both systemically and in the microenvironment of the tumor (Fig. 3).⁴⁵ In addition to producing immunosuppressive molecules such as transforming growth factor β (TGF- β)⁴⁶ and soluble Fas ligand,⁴⁷ many human tumors produce the immunosuppressive enzyme indolamine-2,3-dioxygenase (IDO).^{48,49} This enzyme was previously known for its role in maternal tolerance to antigens from the fetus⁵⁰ and, more recently, as a regulator of autoimmunity that mediates inhibition of T-cell activation.⁵¹ Stereoisomers of 1-methyl-tryptophan inhibit IDO,⁵² and when administered to tumor-bearing mice, they restore immunity and thereby allow immune rejection of the tumor.⁵³ Such stereoisomers might have a role in the treatment of patients with cancer.

The tumor microenvironment can be dominated by regulatory T cells that suppress antitumor effector T cells by producing the immunosuppressive cytokines TGF- β and interleukin-10.⁵⁴ High numbers of these cells can be detected in non-small-cell lung cancer and ovarian cancer.⁵⁵ Murine tumors that produce TGF- β can convert antitumor effector T cells into regulatory T cells, thereby escaping their own destruction by immune cells.^{56,57}

The immunosuppressive effects of a tumor can also be systemic. An increase in regulatory T cells has been observed in the peripheral blood of patients with head and neck cancer^{58,59} or melanoma.⁶⁰ Patients with colorectal cancer or pancre-

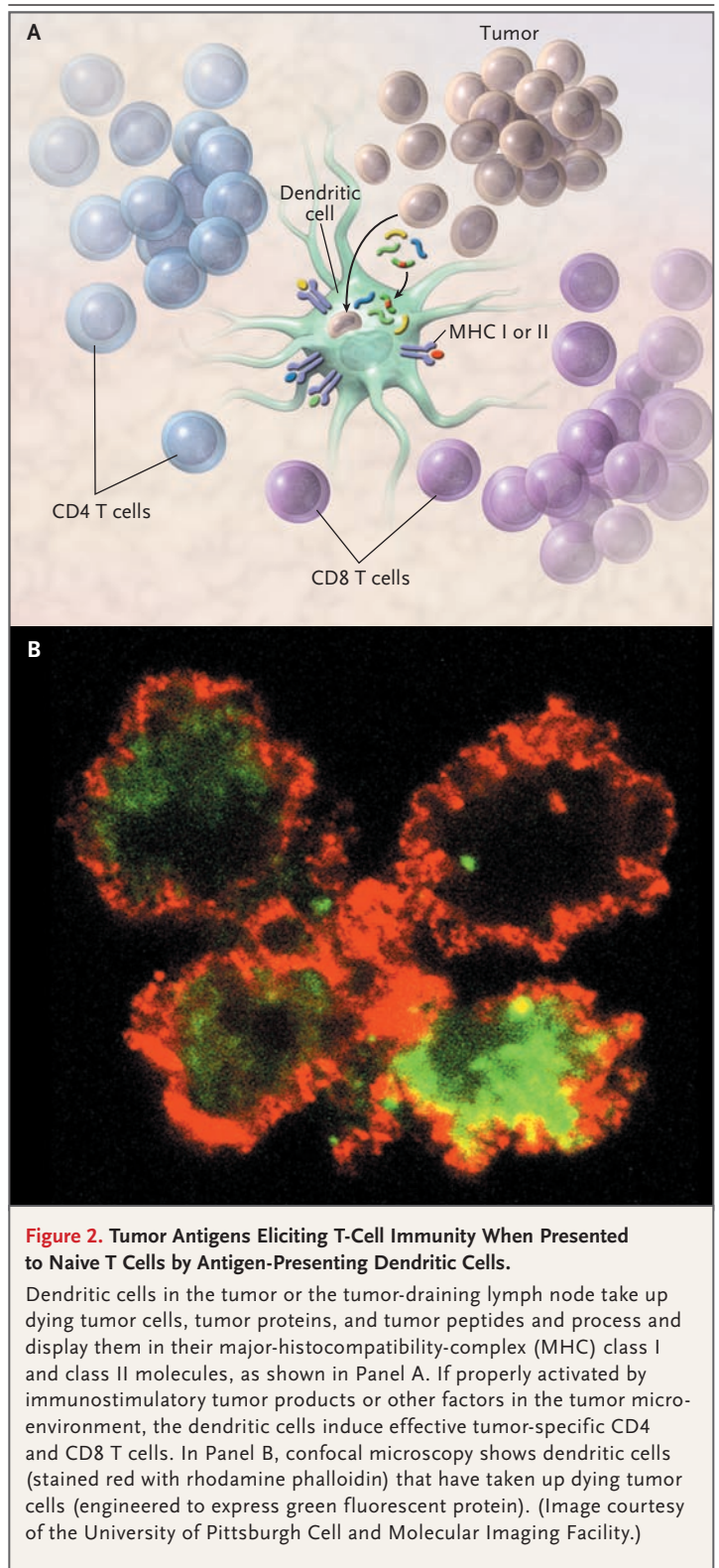


Figure 2. Tumor Antigens Eliciting T-Cell Immunity When Presented to Naive T Cells by Antigen-Presenting Dendritic Cells.

Dendritic cells in the tumor or the tumor-draining lymph node take up dying tumor cells, tumor proteins, and tumor peptides and process and display them in their major-histocompatibility-complex (MHC) class I and class II molecules, as shown in Panel A. If properly activated by immunostimulatory tumor products or other factors in the tumor microenvironment, the dendritic cells induce effective tumor-specific CD4 and CD8 T cells. In Panel B, confocal microscopy shows dendritic cells (stained red with rhodamine phalloidin) that have taken up dying tumor cells (engineered to express green fluorescent protein). (Image courtesy of the University of Pittsburgh Cell and Molecular Imaging Facility.)

Table 1. Immunologic Reagents Approved by the Food and Drug Administration for Cancer Therapy.

Reagent	Reagent Target	Indications
Antibodies		
Trastuzumab (Herceptin)	HER2 receptor	HER2-positive breast cancer
Bevacizumab (Avastin)	Vascular endothelial growth factor	Non-small-cell lung cancer, colorectal cancer, and breast cancer
Cetuximab (Erbix)	Epidermal growth factor receptor	Colorectal cancer and head and neck cancer
Panitumumab (ABX-EGF)	Epidermal growth factor receptor	Colorectal cancer
Ibritumomab tiuxetan (Zevalin)	CD20 B-cell surface antigen (nonradioactive and radiolabeled)	Non-Hodgkin's B-cell lymphoma
Alemtuzumab (Campath)	CD52 lymphocyte surface antigen	Chronic lymphocytic leukemia and T-cell lymphoma
Gemtuzumab ozogamicin (Mylotarg)	CD33 leukemic-cell surface antigen	Acute myeloid leukemia
Rituximab (Rituxan)	CD20 B-cell surface antigen	Non-Hodgkin's lymphoma
Tositumomab (Bexxar)	CD20 B-cell surface antigen (nonradioactive and radiolabeled)	Non-Hodgkin's B-cell lymphoma
Other		
Reagent Type		
Denileukin diftitox (Ontak)	Recombinant interleukin-2 and fragments of diphtheria toxin (binds CD25 receptor on T cells)	Cutaneous T-cell lymphoma
Aldesleukin (Proleukin)	Interleukin-2	Melanoma and renal-cell carcinoma
Interferon alfa-2b (Intron A) and interferon alfa-2a (Roferon-A)	Recombinant interferon	Hairy-cell leukemia, chronic lymphocytic leukemia, Kaposi's sarcoma, melanoma, non-Hodgkin's lymphoma, multiple myeloma, and renal cancer
Imiquimod (Aldara)	Toll-like receptor 7 agonist	Basal-cell carcinoma

atic tumors have increased numbers of activated granulocytes⁶¹ and myeloid-derived suppressor cells,⁶² both of which suppress tumor-specific T cells in mice.^{63,64}

IMMUNOTHERAPY OF CANCER

IMMUNOTHERAPY WITH ANTIBODIES AND T CELLS

The administration of monoclonal antibodies against tumor antigens in HER2-positive breast cancer (trastuzumab),⁶⁵ B-cell lymphomas (rituximab),⁶⁶ and head and neck, lung, and colorectal cancers that express the epidermal growth factor receptor (cetuximab) is clinically effective (Table 1).⁶⁷⁻⁶⁹ Efforts are ongoing to produce antibodies with new effector functions against known targets or to identify new targets for therapeutic antibodies. These targets could be tumor antigens or molecules produced by tumors to promote their own survival, such as vascular endothelial growth

factor⁷⁰ and TGF- β .⁴⁶ Antibodies can also target immune cells at the tumor site to aid the activation of effector cells and promote more effective antitumor immunity.⁷¹

The intravenous administration of tumor-specific autologous T cells that have been grown and expanded *in vitro* is another approach to immunotherapy.⁷² Early experiments in mice showed that T-cell populations that had been cultured with leukemia cells could eradicate an established leukemia *in vivo*.^{73,74} In patients who receive an allogeneic hematopoietic stem-cell transplant, mature T cells in the graft mount a potent antileukemia response.^{75,76} Several groups have pursued this tactic in patients with solid tumors by infusing autologous T cells with specificity for a tumor antigen.

In a phase 1 study, patients with metastatic melanoma were treated with infusions of CD8 T cells that were specific for the melanoma an-

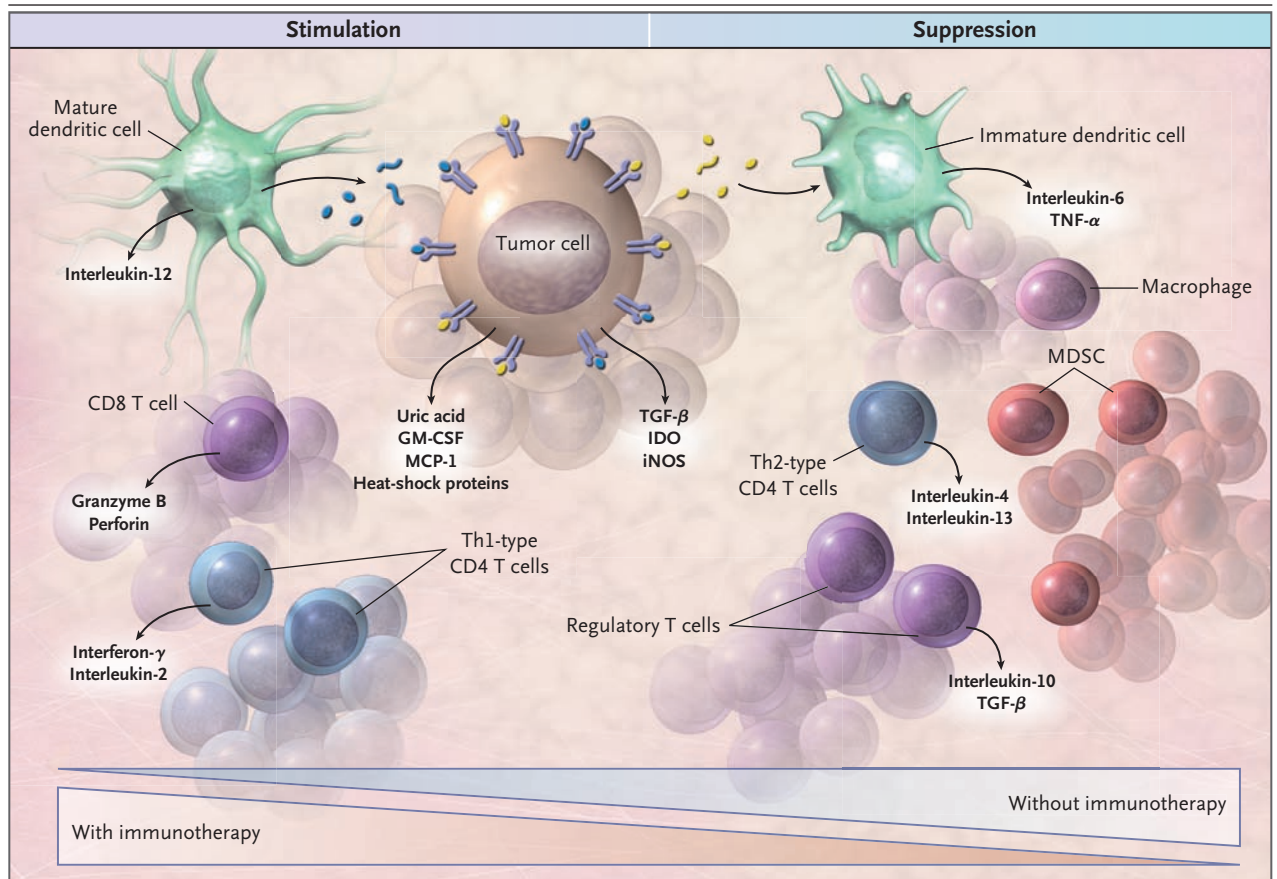


Figure 3. Immunostimulatory and Immunosuppressive Forces in the Tumor Microenvironment.

A growing tumor attracts many components of the host response. Tumor antigens and soluble tumor products attract dendritic cells to the tumor site. These dendritic cells take up tumor antigens, mature into interleukin-12–producing cells, and in the draining lymph node stimulate type 1 helper T-cell (Th1)–type CD4 T cells that produce interferon- γ . These cells help expand the population of CD8 cytotoxic T-lymphocytes that can destroy tumor cells through effector molecules granzyme B and perforin. Another set of tumor antigens and soluble tumor products promote maturation of a different type of dendritic cell that makes proinflammatory cytokines interleukin-6 and tumor necrosis factor α (TNF- α) and give rise to type 2 helper T-cell (Th2)–type CD4 T cells that make interleukin-4 and interleukin-13 and are not effective in tumor rejection. This immunosuppressive environment also promotes generation of regulatory T cells and accumulation of macrophages and myeloid-derived suppressor cells (MDSC). At the time the tumor is diagnosed, the balance between the stimulatory and suppressive forces is in favor of tumor-induced suppression. Immunotherapy that targets the tumor with antibodies and T cells or augments antitumor Th1-type CD4 helper T cells and cytotoxic T lymphocytes with vaccines can tip the balance in favor of immunostimulation. GM-CSF denotes granulocyte–macrophage colony-stimulating factor, IDO indolamine-2,3-dioxygenase, iNOS inducible nitric oxide synthase, MCP-1 monocyte chemotactic protein 1, and TGF- β transforming growth factor β .

tigens MART-1, Melan-A, and glycoprotein 100 (gp100). In 8 of 10 patients, the T cells migrated to tumor sites and caused regression of metastases.⁷⁷ A more recent study in 11 patients with melanoma used T cells specific for Melan-A.⁷⁸ This treatment resulted in one complete and one partial regression. A variation of this therapy was tested by administering nonmyeloablative but lymphocyte-depleting chemotherapy before T-cell infusion.⁷⁹ There were more adverse effects but also greater efficacy. Visceral metastases regressed

in 18 of 35 patients. The most recent modification of this approach was the use of autologous T cells engineered to express T-cell receptors with specificity for MART-1.⁸⁰ The T cells persisted for prolonged periods in 15 patients with melanoma and led to regression in 2 of the patients.

The results of these forms of immunotherapy are marginal, and the effort and cost involved in personalized cellular therapy may not seem justified. However, it is important to note that in phase 1 trials, immunotherapy is tested in patients

with progressive and refractory disease in whom numerous previous therapies have failed. Under these unfavorable circumstances, a marginal success needs to be given weight. The relatively few adverse effects of immunotherapy should support a move toward the use of immunotherapy in earlier stages of cancer.

THERAPEUTIC CANCER VACCINES

Most phase 1 and phase 2 trials of cancer vaccines have involved patients with an extensive cancer burden, impaired immune function, or both.⁸¹ An alternative to infusion of preformed tumor-specific antibodies or T cells, known as passive immunotherapy, is active specific immunotherapy (i.e., cancer vaccines) designed to elicit or boost similar tumor antibodies and T cells in the patient. Some examples are vaccines against breast cancer (the HER2 antigen),⁸²⁻⁸⁴ B-cell lymphoma (the tumor immunoglobulin idiotype),⁸⁵ lung cancer (the MUC1 antigen),⁸⁶ melanoma (dendritic cells loaded with tumor peptides or killed tumor cells),^{87,88} pancreatic cancer (telomerase peptides),⁸⁹ and prostate cancer (dendritic cells loaded with prostatic acid phosphatase).⁹⁰ The results of these trials are encouraging because in each there was evidence of an immune response to the vaccine, and in a few cases there were clinical responses with minimal or no adverse effects.

Regarding the limited number of completed phase 3 trials,⁹¹ most have failed to show a significant benefit with respect to predetermined end points but nevertheless provided information for the design of future trials, especially concerning the choice of patients and stage of disease. The phase 3 trial of a vaccine based on dendritic cells for metastatic, androgen-independent prostate cancer also failed to achieve its primary end point — prolongation of time to disease progression — but median overall survival in the vaccinated group was prolonged by 4.5 months as compared with the placebo group (25.9 months vs. 21.4 months).⁹² The vaccine, sipuleucel T, consists of autologous dendritic cells loaded with a recombinant protein made up of GM-CSF fused to prostatic acid phosphatase. Food and Drug Administration approval of this vaccine awaits confirmatory results from an ongoing phase 3 trial.

The immunosuppressive microenvironment of a tumor stifles the effect of therapeutic vaccines, both during the induction of immunity and in the effector phase of the response. One way to improve

the induction phase is to block the negative regulators of the activation of effector T cells.⁹³ Antibodies against one such molecule, cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4), are being evaluated in clinical trials.^{94,95} CTLA-4 is expressed on activated T cells, where it serves as a brake that halts the activation. Blocking the activity of CTLA-4 allows greater expansion of all T-cell populations, presumably including those with antitumor reactivity. In a recent pilot trial involving 14 patients with hormone-refractory prostate cancer, systemic treatment with anti-CTLA-4 antibody increased antitumor immunity, resulting in a reduction in prostate-specific antigen of more than 50% in two patients and less than 50% in eight patients.⁹⁵ The side effects were rash and pruritus, which required treatment with corticosteroids in the two patients with the best response.

Administration of anti-CTLA-4 antibody simultaneously with cancer vaccines could allow preferential activation and stronger expansion of T cells that respond specifically to the vaccine, thereby enhancing tumor immunity without autoimmunity.^{94,96} Unfortunately, trials that have been conducted so far show that objective cancer regression is accompanied by serious manifestations of autoimmunity. In a trial involving 14 patients with melanoma, combined systemic administration of anti-CTLA-4 antibody with a melanoma gp100 peptide vaccine resulted in a response in 21% of the patients (a complete response in 2 patients and a partial response in 1 patient), but grade 3 or 4 autoimmune manifestations such as dermatitis, enterocolitis, hepatitis, and hypophysitis (inflammation of the pituitary) occurred in 43% of the patients.⁹⁷

Approaches to eliminating immunosuppressive regulatory T cells before vaccination are also being tested. One promising reagent is denileukin diftitox (Ontak, Seragen), a recombinant fusion protein composed of interleukin-2 and diphtheria toxin. It targets the high-affinity interleukin-2 receptor (CD25), which is displayed in abundance by regulatory T cells. When administered to patients with melanoma, this protein depletes the blood of regulatory T cells. In most patients (90%), this treatment has resulted in the production of melanoma-specific CD8 T cells.⁹⁸

Another trial of a vaccine for melanoma used *Pseudomonas* exotoxin A fused to a single-chain Fv fragment of an anti-CD25 antibody to deplete

regulatory T cells before immunization with melanoma-specific peptides from gp100 and MART-1.⁹⁹ Transient depletion of regulatory T cells was observed, but there was no augmentation in the response to the vaccine.

THERAPEUTIC VACCINES COMBINED WITH CHEMOTHERAPY

Integration of immune therapies with standard treatments for cancer is a challenge, especially for cancer vaccines, because of the immunosuppressive effects of most standard treatments. However, explorations of combined treatments are revealing unexpected results. One study compared the outcome of chemotherapy followed by immunization with a cancer vaccine based on the tumor-suppressor protein p53 with chemotherapy alone in advanced small-cell lung cancer.¹⁰⁰ Immunization was started 8 weeks after the completion of chemotherapy. If the tumor progressed, patients were given second-line chemotherapy. Unexpectedly, the response to the second-line chemotherapy was much better in participants who had progression after receiving the vaccine than among those who had progression with chemotherapy alone. A similar observation was made in patients with follicular B-cell lymphoma who were vaccinated with an anti-idiotype vaccine while in remission. When the disease recurred, patients were re-treated with chemotherapy. They had a much higher rate of response to the second round of chemotherapy and a higher rate of a second complete remission than expected for the disease.¹⁰¹

Among postulated mechanisms of the synergistic action of immunotherapy with chemotherapy is elimination of regulatory T cells.¹⁰² Experiments performed in mice more than 20 years ago showed that CD4 suppressor T cells inhibited antitumor immunity, and elimination of such cells by chemotherapy or radiation could improve antitumor immune responses.^{103,104} The improved outcomes in clinical trials of combined treatments are likely to be due at least in part to a similar effect of chemotherapy on regulatory T cells.

IMMUNOPREVENTION OF CANCER

Vaccines against viral antigens such as those of hepatitis B virus and human papillomavirus lower the risk of hepatocellular carcinoma¹⁰⁵ and cervical cancer,¹⁰⁶ respectively, and are part of

large public health endeavors to prevent transmission of these viruses. Should similar vaccines against tumor antigens prove valuable, they could enter clinical practice.¹⁰⁷ Prophylactic vaccines based on autologous tumor antigens may carry a high risk of inducing autoimmunity. Yet testing of such vaccines in genetically engineered mice that express tumor antigens as self molecules clearly shows that the vaccines are effective and safe.¹⁰⁸ The latest example is a vaccine based on the prostate stem-cell antigen (PSCA), which is overexpressed in prostate cancer. This vaccine was effective in preventing prostate cancer in mice that were genetically predisposed to the disease and genetically engineered to express PSCA. The vaccinated mice were alive at 12 months of age, whereas all nonvaccinated mice had died from the tumor by that age.¹⁰⁹ The durable protection was not accompanied by any signs of autoimmunity.

Moving preventive efforts from mouse models to clinical trials is problematic. Evidence of safety and potential efficacy in humans is needed for approval to initiate early-phase trials, yet the results of such trials are needed to provide the required evidence. The solution to this impasse may be to obtain supportive evidence indirectly. A recent case-control study of 705 healthy women and 668 women with ovarian cancer that was undertaken to explore the lifetime risk of ovarian cancer provided such an opportunity. The study showed that a history of mastitis, one or more conditions requiring pelvic surgery, or mumps was associated with a relative risk of 0.31 among women who had four or five such conditions, as compared with a relative risk of 1.0 among women who had had none or only one.¹¹⁰ The tissues affected by these conditions — breast, reproductive organs, and salivary glands — all express the MUC1 tumor self antigen. The study also investigated the likelihood that inflammation accompanying these conditions had provoked an immune response against MUC1 that was later protective against MUC1-positive ovarian cancer. A total of 24.2% of women with IgG anti-MUC1 antibodies had had no conditions or one condition, whereas 51.4% of women who had had four or five of the conditions had anti-MUC1 antibodies (P for trend <0.001). MUC1-based vaccines designed to induce anti-MUC1 IgG antibodies have been tested as cancer therapy, but the efficacy was only marginal,¹¹¹ and such vaccines have

not been tested for cancer prevention because of concern about autoimmunity. This case-control study suggests that, on the contrary, anti-MUC1 immunity appears to be a contributor to beneficial cancer immunosurveillance.

Immunity to other tumor self antigens may also be acquired during events that have no evident relation to cancer. A study of 424 patients with cancer and 375 matched controls revealed that febrile infectious childhood diseases (measles, mumps, rubella, pertussis, and chicken pox) are associated with a reduced risk of most cancers in adulthood.¹¹² Moreover, a multicenter case-control study of 603 patients with melanoma and 627 matched healthy controls¹¹³ showed that a history of severe infectious disease was associated with a reduced risk of melanoma. The odds ratio for a diagnosis of melanoma was 0.37 among the study participants who had had one or more severe infectious diseases, as compared with those who did not have such a history. Studies in mice support the hypothesis that cancer protection induced by infection is mediated by immune responses against

multiple self antigens. Analysis of the antibody repertoire in mice that recovered from infections with vaccinia virus or lymphocytic choriomeningitis virus showed that in addition to antibodies to viral antigens, there were antibodies against cellular proteins, most of which were homologues of previously identified human tumor antigens.¹¹⁴

SUMMARY

Much has been learned about the potential of the immune system to control cancer and the various ways that immunotherapy can boost the potential of the immune system for the benefit of the patient. This knowledge has stimulated the invention of many new therapeutic antibodies, cell-based treatments, and vaccines, which are starting to be used in clinical practice, either alone or in various combinations. These new therapies are expected to result in improved cancer treatment and, eventually, the prevention of cancer.

No potential conflict of interest relevant to this article was reported.

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