

The Next Challenge in Cancer Immunotherapy: Controlling T-Cell Traffic to the Tumor

Jean-Pierre Abastado

Abstract

One of the steps that limits the efficacy of T-cell–based immunotherapy of cancer is T-cell access to the tumor. We recently showed that several chemotherapeutic drugs induce intratumoral expression of chemokines that attract effector T cells. Moreover, in a cohort of patients with melanoma who had been treated with dacarbazine, one of the most frequently used chemotherapies for metastatic melanoma, tumor response to the treatment correlated with intratumoral expression of T-cell–attracting chemokines and with T-cell infiltration. These findings reveal the possibility of developing novel systemic strategies aimed at improving T-cell homing to tumors. Such strategies, used alone or in combination with adoptive T-cell therapies or therapeutic cancer vaccines, may prove to be more efficient in prolonging patient survival. *Cancer Res*; 72(9); 2159–61. ©2012 AACR.

Introduction

Significant progress in the development of therapeutic cancer vaccines has been achieved over the past decade, resulting in 2011 with U.S. Food and Drug Administration approval of the first therapeutic anticancer vaccine, sipuleucel-T (Provenge), for advanced prostate cancer (1). Sipuleucel-T, a preparation of autologous dendritic cells loaded with a recombinant tumor antigen (prostatic acid phosphatase) fused to granulocyte macrophage colony-stimulating factor, induces antitumor T cells and prolongs patient survival. This historical milestone is the outcome of long and arduous efforts to identify suitable tumor-associated antigens (2) and develop strategies to induce appropriate T-cell responses directed against these antigens. To influence disease progression and patient survival, vaccines have to induce a large repertoire of T cells that are able to survive for prolonged periods of time in the circulation. All current vaccination strategies, whether they involve dendritic cells, viral vectors, recombinant proteins, or adjuvant antigenic peptides, induce tumor-specific T cells, sometimes in the majority of cancer patients (3). After vaccination, tumor-specific T cells can account for >3% of all circulating CD8⁺ T cells (4). Yet, only a minority of vaccinated patients actually benefit from the vaccine, indicating that in most cases, tumors progress despite the successful induction of an antitumor immune response (5).

On the other hand, it is now well established that tumor infiltration by T cells, especially Th1 and CD8 T cells, correlates with favorable outcome and prolonged patient

survival (6). It was therefore expected that T-cell induction by therapeutic vaccines would suffice to induce tumor regression, or at least delay the development of metastatic disease and cancer progression. However, this is not the case. It must be concluded that a serious limitation to the efficacy of cancer vaccines results from the poor ability of vaccine-induced T cells to infiltrate the tumors. Very few studies have addressed this question within the framework of a clinical trial. In most trials, induction of T cells is monitored only in the blood, which often poorly reflects the situation at the tumor site(s). Therefore, the ability to control T-cell trafficking is the next challenge in cancer immunotherapy as a critical step toward improving the clinical efficacy of cancer vaccines.

The control of T-cell trafficking to nonlymphoid tissues is determined by a complex network of interactions involving tissue-specific integrins and chemokines with selectins and chemokine receptors expressed on the T cells (7). For example, effector T cells expressing the cutaneous lymphocyte antigen and the chemokine receptor CCR4 home preferentially to the skin, whereas those expressing the $\alpha 4\beta 7$ integrin and CCR9 traffic to the lamina propria of the gut. Whether the same rules apply to T-cell homing to skin and gut tumors is unknown, because tumor vasculature is largely abnormal (8). Nevertheless, it is certain that chemokines are important regulators of T-cell trafficking to the tumors, as shown, for example, in melanoma (9, 10). Chemokines that direct tumor infiltration by T cells may vary according to the target organ. In a mouse model of melanoma, we showed that CD8⁺ T cells infiltrated and controlled visceral metastases but largely ignored cutaneous lesions (10). Surprisingly, however, we found that CXCR3 ligands and CCL5 play a role in this mouse model (the RETAAD model) similar to that observed in patients with melanoma (10) or hepatocarcinoma (11). In mouse and human melanoma, CXCR3 ligands and CCL5 synergize to promote T-cell infiltration into cutaneous lesions. In hepatocarcinoma, we found that

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inflammatory cytokines such as TNF- α and IFN- γ , or TLR ligands, induce the production of CXCL10 (one of the three CXCR3 ligands) and CCL5 in tumor epithelial cells or tumor-infiltrating immune cells. Indeed, in hepatocarcinoma, intratumoral expression of these cytokines and chemokines correlates with T-cell infiltration and prolonged patient survival. Similarly, in an orthotopic mouse model of glioma, Zhu and colleagues (12) showed that TLR3 stimulation favors T-cell infiltration into the tumor by inducing local expression of CXCL10. This striking conservation across species and cancers of different origins is encouraging. Some of the rules that govern T-cell homing to tumors may be quite general and therefore more easily exploitable therapeutically.

By the time a tumor becomes clinically detectable, the cancer cells are likely to have disseminated throughout the body (13, 14). Even in patients who are free of overt metastases at the time of surgery, cancer cells can be detected in various sites, including bone marrow, lung, and kidney (15, 16). Because immunotherapies are intended for use in adjuvant settings, newly induced antitumor T cells have to reach all potential sites of metastasis development. These include, of course, existing metastases but also micrometastases (small clusters of disseminated cancer cells) and metastatic niches, where solitary cancer cells reside in a dormant state for years or decades (17). Therefore, the ideal treatment to augment T-cell homing to these sites would be both systemic and tumor specific.

Even though chemotherapies are widely used in adjuvant treatment of cancers, their precise mechanisms of action *in vivo* remain incompletely understood. Chemotherapeutic drugs were originally selected for their capacity to induce cancer cell death *in vitro*. By inducing irreversible damage to dividing cells, especially to their genome, chemotherapies induce cancer cell apoptosis. However, this is unlikely to fully explain their clinical efficacy, given that high interstitial pressure and low oxygen limit drug penetration and action, and thus not all tumor cells will be exposed to cytotoxic concentrations of the drug (18). It has therefore been proposed that cytolytic drugs are unlikely to control disseminated cancer cells *in vivo* unless they also induce some kind of antitumor immune response (19). The effects of chemotherapies on tumor immunogenicity, T-cell homeostasis, and cancer cell sensitivity to immune effectors have been reviewed elsewhere (20, 21). Their effect on T-cell trafficking may be as important. We showed that some chemotherapies (i.e., dacarbazine, cisplatin, and temozolomide) induce intratumoral expression of T-cell-attracting chemokines (10). In a cohort of patients with melanoma who had been treated with dacarbazine, we observed enhanced chemokine expression and enhanced T-cell infiltration only in tumors that responded to the treatment (10, 22), suggesting that the well-known heterogeneity of melanomas in their sensitivity to chemotherapy could be, in part, ascribed to variable induction of T-cell-attracting chemokines.

Indeed, we and other investigators have frequently observed unexpected synergies between chemotherapy and

immunotherapy (23, 24). Typically, a cancer patient who had been heavily treated with multiple lines of chemotherapy would become resistant and then be included in a vaccine trial. After completion of the vaccinations, as the patient progressed, he or she would be retreated with chemotherapy. Surprisingly, the tumors, which were refractory to chemotherapy before vaccination, would become responsive after vaccination. To explain such paradoxical responses, Lake and Robinson (21) postulated that chemotherapeutic drugs increase the functionality of immune effector cells or augment the sensitivity of cancer cells to the immune effectors. Indeed, cyclophosphamide is known to deplete or inhibit regulatory T cells, and gemcitabine and 5-fluorouracil selectively eliminate myeloid-derived suppressor cells. Doxorubicin, methotrexate, cisplatin, and 5-fluorouracil upregulate death receptors on certain cancer cell lines. Tumor cells treated with genotoxic agents overexpress ligands for activating receptors expressed on NK cells (25). However, none of these mechanisms could operate if T and NK cells did not infiltrate the tumor. Therefore, an alternative explanation for the synergy between chemotherapy and vaccination is that chemotherapy facilitates tumor infiltration by effector T cells induced by the vaccine.

More generally, conversion of tumors into inflamed tissue may help to recruit antitumor immune effectors. Bacillus Calmette-Guérin has been successfully used in the treatment of superficial bladder cancer because it induces a local inflammation (26). Ionizing radiation can induce mouse and human breast cancer cells to express CXCL16, a chemokine that is known to attract CXCR6-expressing Th1 and CD8⁺ T cells (27). The combination of dendritic cell–based vaccination with the multikinase inhibitor sunitinib malate was shown to reduce the level of suppressive cells (Treg and myeloid-derived suppressor cells) and facilitate the recruitment of effector cells in the microenvironment of B16 tumors and their draining lymph node. Of interest, intratumoral expression of CXCR3 ligands was increased by sunitinib and required for the recruitment of CD8⁺ T cells (28). The combination of CTLA-4 blockade and 4-1BB activation was shown to enhance B16 tumor rejection by increasing T-cell infiltration (29). Many available treatments could be tested for such effects. Chemotherapeutic drugs should perhaps be rescreened for their ability to induce expression of T-cell-attracting chemokines. New *in vivo* regimens could be optimized for this property. They would certainly be less toxic, as we found that the drug doses that were required to induce chemokine expression were lower than those that induced cell death (10). To improve cancer vaccines, we need to optimize all steps of the immune response. T-cell trafficking to the tumor must not be overlooked if immunotherapies are to reach their full potential.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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References

1. Kantoff PW, Higano CS, Shore ND, Berger ER, Small EJ, Penson DF, et al. IMPACT Study Investigators. Sipuleucel-T immunotherapy for castration-resistant prostate cancer. *N Engl J Med* 2010;363:411–22.
2. Van Der Bruggen P, Zhang Y, Chau P, Stroobant V, Panichelli C, Schultz ES, et al. Tumor-specific shared antigenic peptides recognized by human T cells. *Immunol Rev* 2002;188:51–64.
3. Liénard D, Rimoldi D, Marchand M, Dietrich PY, van Baren N, Geldhof C, et al. Ex vivo detectable activation of Melan-A-specific T cells correlating with inflammatory skin reactions in melanoma patients vaccinated with peptides in IFA. *Cancer Immun* 2004;4:4.
4. Speiser DE, Liénard D, Rufer N, Rubio-Godoy V, Rimoldi D, Lejeune F, et al. Rapid and strong human CD8+ T cell responses to vaccination with peptide, IFA, and CpG oligodeoxynucleotide 7909. *J Clin Invest* 2005;115:739–46.
5. Rosenberg SA, Yang JC, Restifo NP. Cancer immunotherapy: moving beyond current vaccines. *Nat Med* 2004;10:909–15.
6. Pagès F, Galon J, Dieu-Nosjean MC, Tartour E, Sautès-Fridman C, Fridman WH. Immune infiltration in human tumors: a prognostic factor that should not be ignored. *Oncogene* 2010;29:1093–102.
7. Marelli-Berg FM, Cannella L, Dazzi F, Miranda V. The highway code of T cell trafficking. *J Pathol* 2008;214:179–89.
8. Buckanovich RJ, Facciabene A, Kim S, Benencia F, Sasaroli D, Balint K, et al. Endothelin B receptor mediates the endothelial barrier to T cell homing to tumors and disables immune therapy. *Nat Med* 2008;14:28–36.
9. Harlin H, Meng Y, Peterson AC, Zha Y, Tretiakova M, Slingluff C, et al. Chemokine expression in melanoma metastases associated with CD8+ T-cell recruitment. *Cancer Res* 2009;69:3077–85.
10. Hong M, Puaux AL, Huang C, Loumagne L, Tow C, Mackay C, et al. Chemotherapy induces intratumoral expression of chemokines in cutaneous melanoma, favoring T cell infiltration and tumor control. *Cancer Res* 2011;71:6997–7009.
11. Chew V, Chen J, Lee D, Loh E, Lee J, Lim KH, et al. Chemokine-driven lymphocyte infiltration: an early intratumoral event determining long-term survival in resectable hepatocellular carcinoma. *Gut* 2011;61:427–38.
12. Zhu X, Fallert-Junecko BA, Fujita M, Ueda R, Kohanbash G, Kastenhuber ER, et al. Poly-ICLC promotes the infiltration of effector T cells into intracranial gliomas via induction of CXCL10 in IFN- α and IFN- γ dependent manners. *Cancer Immunol Immunother* 2010;59:1401–9.
13. Hüsemann Y, Geigl JB, Schubert F, Musiani P, Meyer M, Burghart E, et al. Systemic spread is an early step in breast cancer. *Cancer Cell* 2008;13:58–68.
14. Eyles J, Puaux AL, Wang X, Toh B, Prakash C, Hong M, et al. Tumor cells disseminate early, but immunosurveillance limits metastatic outgrowth, in a mouse model of melanoma. *J Clin Invest* 2010;120:2030–9.
15. Pantel K, Alix-Panabières C, Riethdorf S. Cancer micrometastases. *Nat Rev Clin Oncol* 2009;6:339–51.
16. Strauss DC, Thomas JM. Transmission of donor melanoma by organ transplantation. *Lancet Oncol* 2010;11:790–6.
17. Shiozawa Y, Pedersen EA, Patel LR, Ziegler AM, Havens AM, Jung Y, et al. GAS6/AXL axis regulates prostate cancer invasion, proliferation, and survival in the bone marrow niche. *Neoplasia* 2010;12:116–27.
18. Falcon BL, Pietras K, Chou J, Chen D, Sennino B, Hanahan D, et al. Increased vascular delivery and efficacy of chemotherapy after inhibition of platelet-derived growth factor-B. *Am J Pathol* 2011;178:2920–30.
19. Abès R, Gélizé E, Fridman WH, Teillaud JL. Long-lasting antitumor protection by anti-CD20 antibody through cellular immune response. *Blood* 2010;116:926–34.
20. Zitvogel L, Kepp O, Kroemer G. Immune parameters affecting the efficacy of chemotherapeutic regimens. *Nat Rev Clin Oncol* 2011;8:151–60.
21. Lake RA, Robinson BW. Immunotherapy and chemotherapy—a practical partnership. *Nat Rev Cancer* 2005;5:397–405.
22. Nardin A, Wong WC, Tow C, Molina TJ, Tissier F, Audebourg A, et al. Dacarbazine promotes stromal remodeling and lymphocyte infiltration in cutaneous melanoma lesions. *J Invest Dermatol* 2011;131:1896–905.
23. Baxevanis CN, Perez SA, Papamichail M. Combinatorial treatments including vaccines, chemotherapy and monoclonal antibodies for cancer therapy. *Cancer Immunol Immunother* 2009;58:317–24.
24. Antonia SJ, Mirza N, Fricke I, Chiappori A, Thompson P, Williams N, et al. Combination of p53 cancer vaccine with chemotherapy in patients with extensive stage small cell lung cancer. *Clin Cancer Res* 2006;12:878–87.
25. Gasser S, Raulet D. The DNA damage response, immunity and cancer. *Semin Cancer Biol* 2006;16:344–7.
26. Morales A, Eidinger D, Bruce AW. Intracavitary bacillus Calmette-Guerin in the treatment of superficial bladder tumors. *J Urol* 1976;116:180–3.
27. Matsumura S, Wang B, Kawashima N, Braunstein S, Badura M, Cameron TO, et al. Radiation-induced CXCL16 release by breast cancer cells attracts effector T cells. *J Immunol* 2008;181:3099–107.
28. Bose A, Taylor JL, Alber S, Watkins SC, Garcia JA, Rini BI, et al. Sunitinib facilitates the activation and recruitment of therapeutic antitumor immunity in concert with specific vaccination. *Int J Cancer* 2010;129:2158–70.
29. Curran MA, Kim M, Montalvo W, Al-Shamkhani A, Allison JP. Combination CTLA-4 blockade and 4-1BB activation enhances tumor rejection by increasing T-cell infiltration, proliferation, and cytokine production. *PLoS ONE* 2011;6:e19499.

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