

Translational Development of Active Immunotherapy for Hematologic Malignancies

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Abstract

The B-cell tumor-derived Ig receptor may be considered a model tumor antigen for cancer vaccine development. However, as a non-immunogenic, self-antigen, it also must be first rendered immunogenic by chemical or genetic fusion to carriers which enable the induction of protective antitumor immunity in experimental tumor models. Our group has demonstrated that active immunization of human patients with idiotypic protein vaccines containing soluble GM-CSF elicited antigen specific CD8⁺ T cell responses and antitumor effects. An alternative strategy to develop vaccines is the genetic fusion of tumor idiotype-derived single chain antigen with a chemokine moiety. Administration of these vaccines as fusion proteins or naked DNA vaccines may allow more efficient targeting of antigen presenting cells in vivo. Potent antitumor immunity was elicited in mice which was dependent on the generation of specific antibodies and both CD4⁺ and CD8⁺ effector T-cells. We propose that chemokine fusion may represent a novel, general strategy for formulating existing or newly identified tumor and HIV antigens into vaccines for cancer and AIDS, respectively, which elicit potent CD8⁺ T-cell immunity.

The central hypothesis of active immunotherapy of cancer is that either the tumor cell itself or antigens derived from the tumor cell which are specific, or at least selective, for the tumor cell can be modified and injected back into the patient as a therapeutic vaccine. The desired result is activation of both major arms of the immune response, the host antibody response and potentially a host T-cell response. Recently, in support of cancer vaccine development efforts, a large number of potential tumor antigen candidates have been identified for melanomas and solid tumors [1-6]. Increasingly, a number of potential tumor and antigens have also been identified for hematologic malignancies, including minor histocompatibility antigens, HA-1 and HA-2, proteinase-3, and WT1. However, one of the limitations of the cancer vaccine hypothesis is that this experiment has already failed in nature. That is, by virtue of the tumor's clinical appearance, the host immune system has already failed to recognize this growing tumor. Thus, the primary question facing researchers at this point is whether it is even possible to immunize against an inherently weak, self tumor antigen. Therefore, cancer vaccine development, in general, must be focused on answering two independent questions in the proper se-

quence. The first question is a scientific one, whether one can even immunize against a tumor antigen. Answering this scientific question is the goal of most phase I and II cancer vaccine clinical trials.

As one example, lymphomas and myelomas express a tumor-specific antigen which can be targeted by cancer vaccination. The ability of a new idiotype vaccine formulation to elicit T-cell immunity in 20 patients with follicular lymphoma in a homogeneous, chemotherapy-induced first clinical complete remission (CR) was recently studied [7]. Nineteen of the 20 patients tested showed tumor-specific CD8⁺ T-cell responses using autologous tumor targets as the read-out for these assays. In addition, eleven patients had detectable t(14; 18) translocations and were PCR⁺ in the blood both at diagnosis and after chemotherapy, despite being in CR. However, 8 of 11 patients converted to PCR negative after vaccination. Taken together, these results definitively answer the scientific question of whether one can immunize against this tumor antigen. A pivotal, multicenter, controlled, randomized Phase III clinical trial with the clinical endpoint of disease-free survival, was opened in January 2000 to provide the definitive answer to the second major question facing the cancer vaccine

field; namely, can immunization produce clinical benefit? In addition, the analysis of T-cell responses against autologous tumor targets and vaccine administration in a minimal residual disease setting provide general principles relevant to the design of future clinical trials of cancer vaccines in other tumor types.

In addition, high dose chemoradiotherapy followed by reconstitution with autologous or allogeneic stem cells has shown considerable promise as a potentially curable approach to the therapy of lymphomas and myelomas that are otherwise refractory to conventional therapeutic modalities. However, despite advances in supportive care and refinements in the conditioning regimens, persistence of the underlying malignancy remains a major obstacle limiting its success. For this reason, potential strategies for stem cell transplant immunomodulation, and particularly, strategies aimed at enhancing the potential graft antitumor reaction would be desirable.

To test the hypothesis that tumor antigen-specific immunity can be transferred from stem cell donor to recipient, we immunized healthy sibling donors with myeloma IgG, purified from the plasma of their recipients, conjugated to an immunogenic carrier protein, and emulsified in GM-CSF before stem cell transplant [8]. A myeloma idiotype-specific T-cell response was successfully transferred to the recipient as evidenced by: 1) the detection of a lymphoproliferative response which had not been previously detectable before transplantation, 2) the recovery of a recipient CD4+ T-cell line with unique specificity for myeloma idiotype, and 3) the demonstration by in situ hybridization that the cell line was of donor origin. A pilot clinical trial, designed to improve the potency and duration of the transferred idiotype-specific response to recipients is currently in

progress. Donor immunization with tumor-derived idiotype may therefore represent a novel strategy for enhancing the specific antitumor effect of allogeneic stem cell grafts.

References

1. Disis ML, Calenoff E, McLaughlin G, et al. Existent T-cell and antibody immunity to HER-2/neu protein in patients with breast cancer. *Cancer Res.* 1994;54:16-20.
2. Brichard V, Van Pel A, Wolfel T, et al. The tyrosinase gene codes for an antigen recognized by autologous cytolytic T lymphocytes on HLA-A2 melanomas. *J Exp Med.* 1993;178:489-495.
3. Jerome KR, Barnd DL, Bendt KM, et al. Cytotoxic T-lymphocytes derived from patients with breast adenocarcinoma recognize an epitope present on the protein core of a mucin molecule preferentially expressed by malignant cells. *Cancer Res.* 1991;51:2908-2916.
4. Gissmann L, Jochmus I, Nindl I, et al. Immune response to genital papillomavirus infections in women. Prospects for the development of a vaccine against cervical cancer. In: Bystryn JC, Ferrone S, Livingston PO (eds): *Specific Immunotherapy of Cancer with Vaccines. Annals of New York Academy of Sciences*, New York, 1993;690:80-85.
5. Livingston PO, Wong GYC, Adluri S, et al. Improved survival in AJCC stage III melanoma patients with GM2 antibodies: A randomized trial of adjuvant vaccination with GM2 ganglioside. *J Clin Oncol.* 1994;12:1036-1044.
6. Kawakami Y, Eliyanu S, Delgado CH, et al. Cloning of the gene coding for a shared human melanoma antigen recognized by autologous T cells infiltrating into tumor. *Proc Natl Acad Sci USA.* 1994;91:3515.
7. Bendandi M, et al. Complete molecular remissions induced by patient-specific vaccination plus GM-CSF against lymphoma. *Nat Med.* 1999;5:1171-1177.
8. Kwak LW, et al. Transfer of myeloma idiotype-specific immunity from an actively immunised marrow donor. *Lancet.* 1995;345:1016-1020.