Immune Mechanisms Are Major Players in Cancer

Karl Erik Hellstrom and Ingegerd Hellstrom

Department of Pathology, Harborview Medical Center, University of Washington, Seattle, Washington.

Corresponding Author: Karl Erik Hellstrom, Department of Pathology, University of Washington, Harborview Medical Center, 325 9th Avenue, Seattle WA 09104. Phone: 206-897-5907; E-mail: hellsk@u.washington.edu

Running Title: Sipuleucel-T Vaccination

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Summary

Vaccination with sipuleucel-T produced IgG antibodies to secondary prostatic carcinoma antigens and prolonged survival in some patients, and assaying for antibodies may provide prognostic information and identify new vaccine targets. Additional approaches to improve T-cell responses are needed to improve the clinical efficacy.
In this issue of Clinical Cancer Research, GuaThakurta and colleagues (1) demonstrate IgG antibodies to non-targeted tumor antigens in some prostatic carcinoma patients who were vaccinated with sipuleucel-T and showed that the antibodies were associated with improved clinical outcome. Although the clinical efficacy of this treatment was modest, much is being learned from the first human therapeutic cancer vaccine that will lead to more efficacious such vaccines.

After many years of controversy, oncoimmunology is approaching the front-line for cancer therapy. Coley reported over 100 years ago that injection of bacterial toxins into advanced cancers induced a therapeutic response in 40% of cases including the rejection of tumors that were not injected, and Paul Ehrlich speculated over immunological bullets for tumor destruction. Some 50 years later Prehn and others demonstrated that mice immunized against a chemically induced syngeneic tumor rejected transplanted cells from the same tumor, and that the rejection response was primarily mediated by immune lymphocytes. Other studies showed that lymphoid cells in peripheral blood from human cancer patients could recognize and kill the patients' cultured tumor cells also when the patients had advanced disease, and mechanisms which could inhibit this response began to be identified (2). However, controversy prevailed for many years and many argued that spontaneous tumors, including those in humans, cannot be recognized as foreign by the host's immune system and gave "reasons" why therapeutic vaccines cannot work.

The controversies subsided as more refined techniques were developed. Targets of tumor-directed immune responses were identified at the molecular level (3), and insight was gained about immune regulation including the role of costimulation via B7
(CD80; CD86) and CD28 (4). For example, most tumors were found to not express B7 and transfecting them to express B7 dramatically increased their immunogenicity (5). Additional costimulatory receptors (e.g., CD137, OX40) and ligands (e.g., CD137L) were soon identified as were receptors (e.g., CTLA4, PD-1) and ligands (PDL-1, PDL-2) which could inhibit the generation of an immune response. Importantly, manipulation of the immune response by administering monoclonal antibodies (mAbs) to some of these molecules was found to have strong anti-tumor activity in several preclinical models (6-8) including the complete regression and cure of large mouse tumors (9). The discovery of toll-like receptors and their ligands as regulators of innate immune responses provided other approaches to induce a strong anti-tumor response (10). Another important contribution was the demonstration that the tumor microenvironment is highly immunosuppressive and provides an obstacle to therapeutic tumor vaccination.

Cancer cells have a high mutation rate, variants which lack a particular target are common, and selection for therapy resistance is a major concern for the use of anti-cancer drugs. Immune mechanisms have the potential to handle this problem and may even benefit from it, since some mutations encode epitopes that are selective for the individual tumor. A properly engaged anti-tumor immunity can target many different epitopes which decreases the selection of immunoresistant variants. This can be achieved either by using vaccines that comprise many tumor antigens or by inducing an immune response to a primary tumor antigen with strong antigen (epitope) spreading. In the latter case, targeting of the primary antigen induces an immune response including destruction of some tumor cells and the production of immunostimulatory
cytokines/lymphokines which facilitate the maturation of antigen-presenting dendritic cells and the induction of a response also against non-targeted, secondary antigens.

A major event in cancer immunology was the approval by the FDA of sipuleucel-T in 2010 to treat symptom-free patients with metastatic castration resistant prostatic carcinoma. The patients are injected 3 times with their autologous blood lymphoid cells that have been cultured with a fusion protein between prostatic acidic phosphatase (the primary antigen) and GMCSF.

Unfortunately the clinical efficacy of Sipuleucel-T, while statistically significant, is observed in just about 30% of patients and only as a few months prolonged survival without detectable tumor shrinkage. This limited efficacy is in contrast to the therapeutic responses that are seen in some cancer patients (melanoma in particular) after treatment with immunomodulatory monoclonal antibodies (mAbs) such as a combination of anti-CTLA4 plus anti-PD-1 (11). Impressive therapeutic efficacy has also been demonstrated in patients with B cell lymphomas after adoptive transfer of autologous T lymphocytes which have been engineered in vitro to target the tumor and undergo many divisions in vivo (12).

Based on the encouraging findings with immunomodulatory mAbs and engineered T cells we believe that efficacious immunotherapy will be developed also for carcinomas of the prostate. For example, therapeutic vaccination might be combined with immunomodulatory mAbs to decrease the impact of the immunosuppressive tumor microenvironment and the mAbs may perhaps be delivered locally (9).

The report by GuhaThakurta and colleagues (1) is encouraging. It describes ‘blinded’ and Placebo-controlled studies on a large number of randomized patients and
provides stronger evidence than any previous study that antigen spreading, detected as IgG antibodies to secondary tumor antigens, can be induced in some of the patients vaccinated against sipuleucel-T (Fig. 1). Antigen spreading is important since it can dramatically increase the population of lymphoid cells that are engaged in the anti-tumor response. It is noteworthy that those patients where antigen spreading was most pronounced also had the best overall survival. Methods to effectively increase antigen spreading may improve the efficacy of tumor vaccination.

The demonstration of IgG antibodies to secondary antigens that are overexpressed in carcinoma of the prostate is important also by indicating that antibodies to such antigens may serve as prognostic markers. This may be true also for patients undergoing immunotherapy for other tumors, and one should try to find out whether tumor destruction by chemotherapy also can induce antigen spreading. As emphasized by GuhaThakurta and colleagues, an anti-tumor efficacy of the antibodies shall not be dismissed, since antibodies can contribute to tumor destruction, e.g., by mediating ADCC and CDC and/or by interfering with tumor promoting signaling (1). The function of the antibodies needs, indeed, to be investigated.

Since the antibodies were of the IgG isotype, helper T cells were engaged by the vaccination, and published studies, which are discussed by GuhaThakurta and colleagues (1), have demonstrated both CD4 and CD8 cells in patients vaccinated with Sipuleucel-T. However, much more needs to be learned about the cell-mediated responses in the vaccinated patients, since high numbers of tumor-reactive T cells are likely to be needed for immunological destruction of a tumor mass. Has antigen
spreading expanded the number of tumor-reactive Th1 cells to the patients' prostatic carcinomas and are there are clinically feasible ways to further increase this number?

As pointed out by GuhaThakurta and colleagues (1), it may also be rewarding to identify those antigens that most effectively induce an antibody response since they may be good for use as primary target antigens to vaccinate against.

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References


**Figure 1.** Vaccination with PAP in the presence of GMCSF maturates APS and induces an immune response to PAP. Cytokines induced by the response to the primary antigen matures additional APC which take up and present secondary antigens released from killed tumor cells. The tumor microenvironment remains immunosuppressive.
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