Immune Mechanisms Are Major Players in Cancer

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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, GuhaThakurta and colleagues (1) demonstrate IgG antibodies to nontargeted 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 first-line for cancer therapy. Coley (2) 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 (3) speculated over immunological bullets for tumor destruction. Some 50 years later, Prehn and Main (4) 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 that could inhibit this response began to be identified (5). 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 (6), and insight was gained about immune regulation, including the role of costimulation via B7 (CD80; CD86) and CD28 (7). For example, most tumors were found not to express B7 and transfecting them to express B7 dramatically increased their immunogenicity (8). Additional costimulatory receptors (e.g., CD137, OX40) and ligands (e.g., CD137L) were soon identified as were receptors (e.g., CTLA-4, PD-1) and ligands (PD-L1, PD-L2) which could inhibit the generation of an immune response. Importantly, manipulation of the immune response by administering monoclonal antibodies (mAb) to some of these molecules was found to have strong antitumor activity in several preclinical models (9–11), including the complete regression and cure of large mouse tumors (12). The discovery of Toll-like receptors and their ligands as regulators of innate immune responses provided other approaches to induce a strong antitumor response (13). 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 that lack a particular target are common, and selection for therapy resistance is a major concern for the use of anticancer drugs. Immune mechanisms have the potential to handle this problem and may even benefit from it, because some mutations encode epitopes that are selective for the individual tumor. A properly engaged antitumor 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 that facilitate the maturation of antigen-presenting dendritic cells and the induction of a response also against nontargeted, 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 prostate carcinoma. The patients are injected three times with their autologous blood lymphoid cells that have been cultured with a fusion protein between prostatic acidic phosphatase (the primary antigen) and GM-CSF.

Unfortunately, the clinical efficacy of sipuleucel-T, although 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 with the therapeutic responses that are seen in some cancer patients (melanoma in particular) after treatment with immunomodulatory mAbs, such as a combination of anti–CTLA-4 plus anti–PD-1 (14). 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 (15).

Based on the encouraging findings with immunomodulatory mAbs and engineered T cells, we believe that efficacious immunotherapy will also be developed 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 (12).

The study 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 because it can dramatically increase the population of lymphoid cells that are engaged in the antitumor 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 also important, indicating that antibodies to such antigens may serve as prognostic markers. This may also be true for patients undergoing immunotherapy for other tumors, and one should try to find out whether tumor destruction by chemotherapy can also induce antigen spreading. As emphasized by GuhaThakurta and colleagues (1), an antitumor efficacy of the antibodies shall not be dismissed, because antibodies can contribute to tumor destruction, e.g., by mediating antibody-dependent cell-mediated cytotoxicity and complement-dependent cytotoxicity and/or by interfering with tumor-promoting signaling. The function of the antibodies needs, indeed, to be investigated.

Because 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, because 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 because they may be good for use as primary target antigens to vaccinate against.

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