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Therapeutic vaccines

The ultimate personalized therapy?

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Personalized therapy is directed at obtaining maximal therapeutic effect on diseased tissue with minimal off-target side effects. Many classes of therapeutics have attempted to reach this ideal, only to fall well short. Therapeutic vaccines represent a novel class of therapies that can induce a dynamic immune response that, in theory, can continue to adapt and expand following initiation of vaccination. This adaptability, through epitope spreading or antigen cascade, can continuously refine a therapeutic immune response, making it more relevant to the patient's tumor. This active, dynamic, iterative process can continue long after the vaccine course has been completed. Recent clinical trials have provided further insight into the clinical activity of therapeutic vaccines, and offer guidance on clinical expectations following vaccine. The ongoing active sculpting of the immune response, along with the lack of significant side effects, uniquely positions therapeutic vaccines as perhaps the ultimate in personalized therapy.

Keywords: antigen cascade, antigen spreading, epitope spreading, personalized medicine, precision medicine, immunotherapy, individualized therapy, cancer vaccine

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Introduction

The ideal medical intervention aims to correct an underlying disorder or condition with minimal or no negative impact on health. Initial systemic anticancer regimens employed chemotherapy agents that were able to kill cancer cells but in many cases did not lead to cures. Unfortunately, these agents have harsh side effects with very narrow therapeutic indices. Recently, attention has shifted substantially to "personalized medicine" or "precision therapy," with a rapid surge in the number of agents that target specific pathways involved in oncogene addiction. Unfortunately, current treatment strategies under the rubric of personalized therapy frequently fall far short of the ideal goal of targeting only diseased tissues without side effects on normal tissues. Furthermore, there are often numerous driver mutations within a cancer cell, with new mutations coming into play over time, requiring that multiple pathways be blocked concurrently and sequentially. Thus, with few exceptions, this form of targeted therapy has not led to dramatic improvements in patient outcomes.

While therapeutic vaccines have only recently demonstrated the potential to improve patient outcomes, as a class they have the potential to become the ultimate in personalized medicine. Although therapeutic vaccines for tumor-specific antigens (e.g., mutated ras or idiotypic vaccines) may intuitively be thought of as personalized therapy, vaccines against widely shared tumor-associated antigens (e.g., PSA, MUC-1 or CEA) may also give rise to a personalized therapeutic response. These therapeutic vaccines, which have few if any side effects, can initiate a therapeutic response that the resilient, adaptable immune system can further expand into an ongoing, dynamic immune response—arguably the optimal personalized therapy.

Understanding the "New Kid"

Therapeutic vaccines have a completely different mechanism of action compared with previously approved cancer therapeutics.

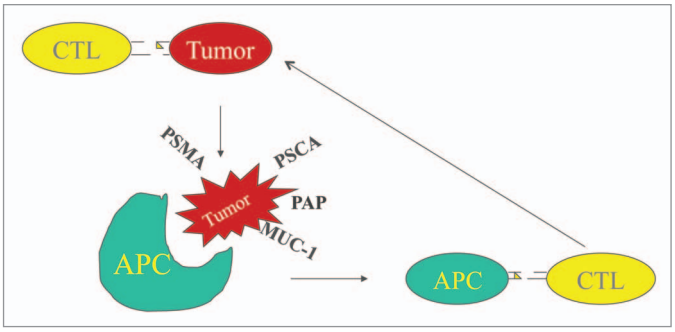

Figure 1. Antigen cascade: An initial immune response (e.g., a PSA-specific cytotoxic T lymphocyte [CTL] following vaccination with a PSA-specific vaccine) may encounter a PSA-expressing tumor cell. If that CTL can kill the tumor cell in an immunologically relevant manner, as that tumor cell is dying it can be taken up by antigen-presenting cells (APCs). There, other tumor-associated antigens (depicted by prostate-specific membrane antigen [PSMA], prostate stem cell antigen [PSCA], prostatic acid phosphatase [PAP] and mucin-1 [MUC-1]) can be processed and presented via cross-presentation to other CTLs, a process that can activate these CTLs specific for these other antigens. Thus, while the initial vaccine may target one antigen, a broader antitumor immune response may ensue, and this dynamic response may continue to broaden and adapt to subsequent mutations.

First, vaccines do not directly target the tumor or its microenvironment, but instead directly target the immune system, which subsequently initiates or expands attacks on the tumor. Furthermore, a cytotoxic therapy does not initiate a memory response, whereas such a response is an important goal of an effective therapeutic vaccine. Thus, the kinetics of a clinical response following treatment with a therapeutic vaccine are predictably different from the kinetics of a cytotoxic agent.[1-4] Indeed, because of their very different mechanisms of action, therapeutic vaccines initiate an ongoing, dynamic response that may result initially in subtle changes to the tumor growth rate; over time, however, if these changes are maintained or expanded, improvements in outcome may be substantial. In other words, the immune response may start slowly, but over time it may grow deeper, broader, and more clinically active, and may persist long after initial administration of the vaccine. Underscoring this important point, definitive clinical trials with two immunotherapies, ipilimumab[5] and sipuleucel-T,[6] have demonstrated no improvement in median progression-free survival, but have shown substantial improvement in overall survival.

The Winning Strategy

Multiple preclinical studies have suggested that $CD8^+$ T cells are key players in the antitumor response following therapeutic vaccines. CD8 depletion studies demonstrate complete abrogation of the therapeutic effect of vaccines. Thus, many studies have focused on increasing the number of $CD8^+$ T cells following vaccination. However, focusing on the absolute number of vaccine-specific T cells misses other critical factors, such as the quality of the T-cell response and the effectiveness of the cancer patient's own immunosuppressive entities.

Many immunosuppressive factors and cells within the tumor microenvironment can significantly affect the success of a therapeutic vaccine.[7] This is one reason that many studies have suggested that immunotherapy should ideally be used earlier in the disease course in patients with lower tumor burdens.[8,9] Other studies have suggested combining vaccine with standard therapies in a manner designed to minimize or neutralize the immunosuppressive factors elaborated by or harbored within the tumor.[10-12] (The myriad important features of the tumor microenvironment, and their negative impact on the function of antitumor T cells, is beyond the scope of this brief commentary.)

The quality of a T-cell response may arguably be divided into two aspects. The first is the avidity of the T-cell response. The avidity of a T cell can be defined by the concentration of antigen required to elicit a response. Thus, higher-avidity T cells can become activated to kill tumor cells with much lower concentrations of antigen.[13] This is important because only high-avidity T cells can efficiently kill tumor cells. Therefore, therapeutic vaccine strategies designed to augment antitumor avidity may prove to be more clinically active. Unfortunately, most conventional T-cell assays, such as the ELISPOT or tetramer, do not measure this important factor.

The second qualitative aspect of a T-cell response is its breadth, or the expansion of a T-cell response to epitopes not found in the vaccine. This concept, known as epitope spreading, antigen spreading or antigen cascade,[14] has been associated with both MHC class I- and II-restricted responses and reflects cross-presentation of tumor antigens. Thus, if a tumor-specific T cell can lyse tumor cells, the dead or dying tumor cells can be taken up by antigen-presenting cells, with the result that multiple, perhaps even more immunogenic, tumor antigens can be presented to immune cells, initiating a broader immune response (**Fig. 1**).

This phenomenon has been described by many investigators, but a recently published preclinical study by Hodge et al. highlights the impact of antigen cascade.[15] In this study, mice implanted in the flank with a CEA-expressing tumor were vaccinated subcutaneously with a CEA-based vaccine. In the opposite flank, a parental tumor that did not contain CEA was implanted. Thus, an immune response to the CEA antigen in the vaccine could not directly affect the growth of the CEA^- tumor. In this experiment, vaccinated mice had a substantial decrease in tumor size in both the CEA^+ and CEA^- tumors compared with nonvaccinated mice. In fact, the antitumor immune response appeared to be due to T cells specific for GP70, an endogenous murine retroviral antigen present in the tumors implanted in both flanks, but not included in the vaccine. Indeed, in vaccinated mice, the IFN-γ response to GP70 was about 15 times greater than the response to the CEA present in the vaccine, suggesting that this cascade response was critical to the activity of the vaccine in this model.

In humans, it is possible that the same vaccine may induce completely different

immune responses, in terms of antigen cascade, in different patients with the same type of cancer. Furthermore, as suggested in the murine model described above, the immune response to antigens not present in the vaccine may be much more clinically relevant for a given patient than the initial immune response to the epitope in the vaccine. However, while antigen cascade may be a significant factor in a clinically relevant antitumor immune response,[14] using conventional T-cell assays to determine a priori which antigen-specific T cells are most likely to be activated, and which of those is clinically significant, is akin to finding the proverbial needle in a haystack.

An expanding, cascading immune response may continue over time, eventually broadening into an immune response that could be even more clinically relevant than the initial immune response to vaccine. Many clinical trials of therapeutic vaccines in cancer patients have reported multiple examples of T-cell antigen cascade.[16-20] Some studies have also suggested improved clinical outcomes for patients who demonstrated a broadened immune response to epitopes not found in the vaccine.[19,20]

Implications for Personalized Therapy

The phenomenon of antigen cascade means that a patient treated with a therapeutic vaccine could potentially generate an immune response tailor-made to his or her individual tumor—a response that may be more clinically relevant than the response to the epitope found in the vaccine. Furthermore, unlike with traditional therapies, an ongoing, dynamic immune response can adapt to subsequent mutations within the tumor, continuing or expanding a therapeutic response. The built-in ability of an immune response to adjust to changes within the tumor, to target mutations (which may be much more immunogenic than tumor-associated antigens), and to develop higher-avidity T-cell responses over time, may very well provide the best opportunity for personalized medicine. A lack of significant side effects, along with our growing understanding of when to use this modality and what clinical outcomes to look for, indicate a bright future for therapeutic vaccines in our increasingly more sophisticated, and from a patient standpoint, better tolerated, fight against cancer.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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