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Cancer immunotherapy: Moving forward with peptide t cell vaccine

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Abstract
Many new therapies are currently being used to treat cancer. Among these, chemotherapy based on peptides has been of great interest due to the unique advantages of peptides, such as a low molecular weight, the ability to specifically target tumor cells, and low toxicity in normal tissues. In treating cancer, peptide-based chemotherapy can be mainly divided into three types, peptide-alone therapy, peptide vaccines, and peptide-conjugated nanomaterials. Peptide-based vaccines have been used in advanced cancers to improve patients overall survival. The combination of peptides with nanomaterials expands the therapeutic ability of peptides to treat cancer by enhancing drug delivery and sensitivity. Immune recognition and elimination of cancerous cells is the primary goal of cancer immunotherapy. However, obstacles including immune tolerance and tumor-induced immunosuppression often limit beneficial immune responses. Vaccination is one proposed intervention that may help to overcome these issues and is an active area of study in cancer immunotherapy. Immunizing with tumor antigenic peptides is a promising, vaccine strategy hypothesized to boost pre-existing antitumor immunity. However, tumor antigens are often weak T cell agonists, attributable to several mechanisms, including immune self-tolerance and poor immunogenicity of self-derived tumor peptides. One strategy for overcoming these mechanisms is vaccination with mimotopes, which alter the antigen presentation and/or T cell activation. Peptide vaccines incorporate one or more short or long amino acid sequences as tumor antigens, combined with a vaccine adjuvant. Thus, they fall broadly into the category of defined-antigen vaccines, along with vaccines using protein, protein subunits, DNA, or RNA.

Keywords: peptide, t cells, peptide vaccines, antigen vaccines

Introduction
Current comprehensive cancer care is centered on reducing the bulk of disease through surgery, chemotherapy, and radiation. Despite the increasing effectiveness of these cornerstones of treatment and high cure rates of multiple cancer forms, cancer remains a leading cause of death [1]. Recent breakthroughs in cancer immunotherapy have added several promising new therapies to the traditional armamentarium of oncology treatment regimens.

The strategy of utilizing the immune system in the treatment of cancer dates back to the 1890s and the work of William Coley [2]. Coley observed that some tumors regress in the setting of acute bacterial infection. He attempted to recapitulate this phenomenon by studying the injection of heat-inactivated *Streptococcus erysipelas* and *Serratia marcescens* (Coley's toxins) in cancer patients. The field of cancer immunology and immunotherapy has greatly advanced since Coley's initial studies, a time when little was known about the mechanisms underlying the antitumor effects of bacterial toxins. There is now a growing understanding of how the immune system identifies tumor cells and targets them for elimination. Just as important is the growing understanding of how tumors can undermine the immune system's ability to recognize and eliminate cancer cells.

Briefly, an adaptive immune response against tumor cells is classically believed to be initiated when tissue-resident antigen-presenting cells, such as dendritic cells, take up and process tumor-specific or tumor-associated antigens, and present these antigens in the context of major histocompatibility complex (MHC) complexes to naïve T-cells in secondary lymphoid organs. Naïve T-cells can differentiate and expand into different classes of antigen-specific T-cells, including cluster of differentiation (CD) 4^+ T helper cells and $CD8^+$ effector cytotoxic T lymphocytes (CTLs). At each step of this process, various signals shape whether an antitumor T-cell response will be produced, or conversely, an immunosuppressive and/or tolerogenic response will be made by such mediators as regulatory T-cells and myeloid-derived suppressor cells (reviewed by Palucka and Banchereau [3], Chen and Mellman [4]. and Blattman and Greenberg) [5]. Immunotherapies for cancer can target each or many of these steps to skew toward an antitumor response and away from an immunosuppressive response.

Cancer immunotherapies can be categorized as non-antigen-specific or antigen-specific therapies. Non-antigen-specific immunotherapies aim to either enhance the immune response in a general fashion or to decrease the immunosuppression present in the tumor environment. Non-antigen-specific therapies include cytokines and immune growth factors (eg, interferon (IFN]-α, interleukin [IL]-2, or granulocyte

macrophage colony-stimulating factor), immunologic adjuvants (eg, Bacille Calmette-Guérin); Toll-like receptor (TLR)-3 agonists, such as poly-I:C (Rintatolimod, Ampligen®; Hemispherx Biopharma, Inc., Philadelphia, PA, USA) and poly-ICLC (Hiltonol®; Oncovir, Washington, DC, USA); TLR-4 agonists, such as monophosphoryl lipid A; the TLR-7 agonist, imiquimod; immune checkpoint blockers, eg, anticytotoxic T-lymphocyte antigen-4 (CTLA-4) antibody [6, 7] and the programmed death-1 (PD-1) pathway agents, nivolumab and lambrolizumab [8, 53-55].

Compared with non-specific immunotherapies, antigen-specific therapies, such as therapeutic vaccines against cancer, aim to induce immune cells to target cancer cells that express a particular set of antigens. Different classes of cancer vaccines include peptide-based or protein-based vaccines, cancer cell-based vaccines, viral vector vaccines, DNA vaccines, messenger RNA vaccines, and carbohydrate vaccines [56-63]. In all cases, these vaccines involve two components, an antigen and an adjuvant, aimed at promoting local inflammation and the resulting immunization. Additionally, all of the above types of cancer vaccines rely on the patients' endogenous dendritic cells (DCs) for their uptake and effective antigen presentation to tumor-specific $CD8^+$ and $CD4^+$ T-cells.

Another category of cell-based cancer vaccines is use of patients' ex vivo-generated and tumor antigen-loaded DCs (or more precisely, autologous cellular therapeutics). This strategy limits the dependence of the immune system on patients' resident DCs, which have been shown to be defective in the advanced stages of cancer [3, 20, 21] or even redirected to differentiate toward myeloid-derived suppressor cell. Regardless of whether endogenous or ex vivo-generated DCs are utilized for immunization, therapeutic cancer vaccines need to overcome several common challenges to induce immunity in the presence of established tumors and can benefit from recent developments in the area of DC biology [23, 24].

Undoubtedly, vaccines are effective in preventing infections by recruiting various components of the immune system against numerous pathogens. Since the immune system has the ability to recognize transformed malignant cells and limit tumor growth, immunotherapy has now become an effective way to treat cancer. Amongst various components of the immune system T cells and in particular CD8 cytotoxic T lymphocytes (CTLs) are the most effective elements in recognizing alterations occurring in transformed cells. The antigens recognized by T cells correspond to peptides that associate MHC molecules. Such peptides result from processed proteins from the infectious microorganisms or derived from abnormally expressed gene products in malignant cells. Tumor-reactive T cells are frequently present in cancer patients in the form of tumor-infiltrating lymphocytes (TILs). However, *ex vivo* TIL expansion and reintroduction into the patients has demonstrated remarkable therapeutic effects in some patients. Unfortunately TIL therapy is technically challenging, expensive and not all cancers contain TILs. Thus, there is a critical need for other means to generate tumor reactive T cells with a simpler and more cost effective strategy such as vaccination.

Discussion

Monoclonal antibodies (mAbs) have already become an important part of the treatment for many cancers. As researchers have learned more about what makes cancer cells different from normal cells, they have developed mAbs to exploit these differences. They have also developed newer forms of mAbs, attaching them to drugs or other substances to make them more powerful.

Recent US Food and Drug Administration approvals of Provenge® (sipuleucel-T) as the first cell-based cancer therapeutic factor and ipilimumab (Yervoy®/anticytotoxic T-lymphocyte antigen-4) as the first "checkpoint blocker" highlight recent advances in cancer immunotherapy. Positive results of the clinical trials evaluating additional checkpoint blocking agents (blockade of programmed death [PD]-1, and its ligands, PD-1 ligand 1 and 2) and of several types of cancer vaccines suggest that cancer immunotherapy may soon enter the center stage of comprehensive cancer care, supplementing surgery, radiation, and chemotherapy.

The immune system has checkpoint proteins (such as PD-1 and CTLA-4) that help keep it from attacking other normal cells in the body. Cancer cells sometimes take advantage of these checkpoints to avoid being attacked by the immune system.

Targeting these checkpoints is quickly becoming an important part of the treatment for some cancers, including melanoma and non-small cell lung cancer. Researchers have also found promising early results against a number of other cancer types. Unlike most other cancer drugs, these checkpoint inhibitors seem to be helpful against many different types of cancer.

A newer approach being studied is to combine treatments that have different targets (such as nivolumab, which targets PD-1, and ipilimumab, which targets CTLA-4) to see if this might work better. In melanoma, this combined approach has been shown to work better than using either treatment alone, but the combination also comes with an increased risk of serious side effects.

Some of the more common types of cancer in which vaccines are now being studied include

- Brain tumors (especially glioblastoma)
- Breast cancer
- Cervical cancer
- Colorectal cancer
- Kidney cancer
- Lung cancer
- Lymphoma
- Melanoma
- Pancreas cancer
- Prostate cancer

Endogenous responses to tumor antigens are detected in both the peripheral blood and tumor of many patients with cancer [32]. Although detectable, endogenous T cells typically fail to control tumor growth. Augmenting T cell responses through vaccination is one strategy to improve anti-tumor immunity. Several vaccine strategies have been studied, including whole-tumor cells irradiated and modified to express immune

modulating cytokines, full-length proteins, autologous DC vaccines pulsed with antigen, and synthetic peptide vaccines [33]. Vaccination as a treatment modality for cancer has resulted in suboptimal success until recently with the first FDA-approved vaccine for hormone-resistant prostate cancer, Sipuleucel-T (Provenge), which extended the life of these terminal patients by 4 months in a Phase III clinical trial [34]. Although a success for cancer immunotherapy, Provenge is a costly and patient-specific autologous cell-based vaccine, causing concern about its practicality as a long-term treatment solution. Alternatively, synthetically derived peptides consisting of known epitopes for CD8+ cytotoxic T cells have been tested in numerous cancer vaccines [27]. While limited by identification of appropriate MHC haplotypes for each epitope, peptide vaccines are less costly, straightforward to produce, safe, and responding T cells can be readily monitored by MHC multimers or stimulation assays [27].

Types of vaccines

Many different types of vaccines are now being studied to treat a variety of cancers.

Tumor cell vaccines

These vaccines are made from actual cancer cells that have been removed from the patient during surgery. The cells are altered (and killed) in the lab to make them more likely to be attacked by the immune system and then injected back into the patient. The patient's immune system then attacks these cells and any similar cells still in the body.

Most tumor cell vaccines are *autologous*, meaning the vaccine is made from killed tumor cells taken from the same person in whom they will later be used. Other vaccines are *allogeneic*, meaning the cells for the vaccine come from someone other than the patient being treated. Allogeneic vaccines are easier to make than autologous vaccines, but it's not yet clear if one type works better than the other.

Antigen vaccines

These vaccines boost the immune system by using only one antigen (or a few), rather than whole tumor cells. The antigens are usually proteins or pieces of proteins called *peptides*.

Antigen vaccines can be specific for a certain type of cancer, but they are not made for a specific patient like autologous tumor cell vaccines are.

Dendritic cell vaccines

These vaccines have shown the most success so far in treating cancer. Sipuleucel-T (Provenge), which is approved for the treatment of advanced prostate cancer, is an example of a dendritic cell vaccine.

Dendritic cells are special immune cells in the body that help the immune system recognize cancer cells. They break down cancer cells into smaller pieces (including antigens), and then hold out these antigens so other immune cells called T cells can see them. The T cells then start an immune reaction against any cells in the body that contain these antigens.

Dendritic cell vaccines are made from the person in whom they will be used. The process used to create this type of vaccine (known as an *autologous* vaccine) is complex and expensive. Doctors remove some immune cells from the patient's blood and expose them in the lab to cancer cells or cancer antigens, as well as to other chemicals that turn the immune cells into dendritic cells and help them grow. The dendritic cells are then injected back into the patient, where they should cause an immune response to cancer cells in the body.

Vector-based vaccines

These vaccines use special delivery systems (called *vectors*) to make them more effective. They aren't really a separate category of vaccine; for example, there are vector-based antigen vaccines.

Vectors are special viruses, bacteria, yeast cells, or other structures that can be used to get antigens into the body. The vectors are often germs that have been altered to make sure they can no longer cause disease.

Vectors can be helpful in making vaccines for a number of reasons. First, they can be used to deliver more than one cancer antigen at a time, which might make the body's immune system more likely to mount a response. Second, vectors such as viruses and bacteria might trigger their own immune responses from the body, which could help make the overall immune response even stronger. Finally, these vaccines might be easier and less expensive to make than some other vaccines.

Mimotopes

Although touted for specificity, T cell receptors associate with different but related MHC

Molecules or peptide antigens [7, 8]. T cell cross-reactivity can be exploited to generate desired immune responses using mimotopes. Mimotopes, also referred to as analog peptides, variant peptides, heteroclitic peptides, or altered peptide ligands, are mimics of peptide epitopes, which can augment or antagonize T cell responses. Mimotopes contain amino acid substitutions in the peptide sequence that can improve peptide-binding affinity for the MHC [82] and/or alter the interaction of the pMHC–TCR complex [35-38]. Although notyet perfected, the intention is that vaccination with mimotopes with strategic amino acid substitutions will result in predictable T cell responses toward a desired antigenic specificity.

Conversely, in cancer immunotherapy, the goal of isotopes is to enhance tumor-specific T cell expansion and functional recognition of tumor cells. Mechanisms that limit auto reactive T cell responses, often prevent sufficient T cell responses to self-TAA. Relative to vaccination with native tumor antigens, mimotopes are often more immunogenic, which increases the expansion of antigen-specific T cells. Thorough examinations of the responses to the gp1002M mimotope in humans, the AH1 mimotopes in mice, and others have been reported. Mimotopes may also alter the TCR binding surface, which can affect the quality and repertoire of the responding T cells. The goal of stimulating T cells with mimotopes is to generate increased expansion of T cells with high avidity for tumor antigens. However, the mimotope may also stimulate T cells that do not recognize the native tumor antigen or T cells that interfere with the intended response, which are necessary considerations for rational improvements of mimotope vaccines.

Advantages of peptide vaccines

There are several advantages of peptide vaccines over other cancer vaccine approaches. Aside from the ease of synthesizing them, and their safety demonstrated in many trials, they have been effective at inducing T cell responses. Short peptides (typically nine amino acid residues) bind to Class I MHC molecules and induce CD8 T cells that can lyse melanoma cells expressing the cognate MHC and peptide. Immune response rates vary, depending on the peptides and adjuvants used, and depending on the assay method. However, immune response rates approaching 100% can be achieved [28, 29-31] and the proportion of CD8+ cells responding to individual peptide antigens can exceed 1%. Though MHC-restriction of individual peptides limits their use to a subset of patients, we have found that mixtures of a dozen peptides restricted by HLA-A1, A2, A3, or A11 can be prepared as a stable mixture and can induce immune responses in the 85% of patients with melanoma who express one or more of those MHC molecules [10], without negative effects from competition among the peptides [4]. Other experience supports the ability to induce T cell responses to multiple peptides when vaccinating with peptide mixtures.

Limitations of peptide vaccines

Short peptides restricted by Class I MHC molecules can bind directly into the peptide binding groove on the exposed surface of the appropriate Class I MHC molecule. In vivo, when a peptide vaccine is administered into the subcutaneous tissue (or other sites), the peptides may be able to bind to numerous types of cells, only a few of which are professional APC. When they bind to non-professional APC (e.g. fibroblasts), they are presented without optimal co-stimulation; presentation of antigen in this way can even be toleragenic. Thus, there is concern that the effectiveness of vaccination with short peptides may be limited by this phenomenon. Also, these short peptides have little or no tertiary structure and thus are subject to rapid degradation by tissue and serum peptidases. It is possible that the low magnitude and transience of T cell responses observed in many patients vaccinated with short peptides may be explained in part by rapid degradation of these peptides in vivo, before they can be presented by professional APC, and also by suboptimal antigen presentation when it occurs. Another factor is that when a vaccine is administered in the skin, it is generally believed that antigen presentation depends on dendritic cells bearing the antigen to migrate to the regional draining nodes and to present the antigen there to naïve circulating lymphocytes. When an antigen is presented by dendritic cells (DC) that have taken up a whole protein or DNA, the peptide of interest is going to be presented on an ongoing basis because it is generated inside the cell over time and presented on MHC. However, when a short peptide is used, and its ability to be presented to T cells in the draining node depends on its ability to remain bound to the MHC; so short peptides with low affinity for the MHC may be less immunogenic than they would be if they were more continuously being presented, for which one example may be gp100280-288.

Challenges in therapeutic cancer vaccination

For a therapeutic cancer vaccine to be effective, it must be capable of inducing a high number of antigen-specific T-cells against an established tumor, which can migrate to the tumor and perform their effector functions at the tumor site. However, challenges are present for each of these three goals. The first challenge is achieving high numbers of antitumor T-cells when the vaccine is being administered in the presence of an ongoing, although dysfunctional, immune response. Due to the ongoing antitumor immune response, the vaccine-carrying antigen-presenting cells, may be recognized by the $CD8^+$ T-cells as "tumor". Since this encounter occurs in the periphery, away from the immunosuppressive tumor microenvironment, the $CD8^+$ T-cells may be capable of eliminating the vaccine, and thus limiting the vaccine's effectiveness before it can induce an immune response. Additionally, there is a lack of the proinflammatory signals required to promote effective immune responses. These signals are replaced by tumor-induced immunosuppressive/ Anti-inflammatory signals predominating in cancer patients. Therefore, to achieve the goal of inducing high numbers of tumor-specific T-cells, the vaccine-carrying antigen-presenting cells must not only survive long enough to present antigen, but must also provide the inflammatory signals to drive effector cell functions.

Conclusion

Several of the new cancer vaccines have recently shown promise in prolonging patient survival. The next era of vaccine development is likely to involve both continued improvement of the vaccines themselves as well as combinatorial application of vaccines with agents that target the tumor microenvironment to promote entry of vaccination-induced cells, while eliminating local predominance of suppressive cells, and amplifying and prolonging the duration of the effector phase of antitumor immunity at tumor sites. The development of optimized immunotherapies for advanced cancer will also benefit from identification of the most relevant laboratory correlates of clinical effectiveness and integration of immunotherapy with other elements of comprehensive cancer care.Peptide-based vaccination against neoplastic diseases has made enormous progress and remains an active and crucial area of investigation, holding promise for improving the clinical outcome in cancer patients. However, several hurdles need to be overcome. The most important one, in our opinion, is the ability of tumor cells to evade a strong tumor-specific immune response [26]. There are several potential ways to avoid the escape of tumor cells. First, patients with early-stage disease could be vaccinated to cope with immune tolerance or immunosuppression caused by factors released by tumor cells. Second, multi-epitope vaccines could be used to bypass the heterogeneity in TAA expression. Third, cytokine adjuvants, such as GM-CSF, could be used to recruit DCs at the vaccination site and improve TAA presentation. IL-2 and/or IL-12 given systemically could be used to help to expand antitumor T cells. IL-2 could be used to restore the function of patients' T cells. Fourth, the expression of peptide-MHC complexes on target cells could

be increased by the systemic administration of IFN- or IFN-. Finally, as indicated by many studies in animal models and in humans, classII-restricted HLA epitopes should be provided, even in the formof promiscuous determinants [9], to augment the strength and duration of the immune response. It may be premature to declare that cancer vaccines are an effective antitumor approach. However, we may be optimistic about the clinical use of peptide-based cancer vaccines. In fact, the many hurdles on the way to a successful clinical application are now identified and, therefore, may be overcome in the near future. However, we should not "down-regulate" our criticism on the whole issue of cancer vaccines. Unorthodox but scientifically sound views [25] should not be ignored so that we can temper our enthusiasm and avoid undue hype in the interest of cancer patients.

Abbreviations

MHC: Major Histocompatibility Complex
CTLs: Cytotoxict Lymphocytes
TLR: Toll-Like Receptor
CTLA: 4 - Anticytotoxic T-Lymphocyte Antigen-4
TIL: Tumour Infiltrating Lymphocytes
Tags: Tumour Antigens
FDA: Food and Drug Administration

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