Cancer Drug Discovery and Development

Ena Wang
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Developments in T Cell Based Cancer Immunotherapies

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Preface

After decades of disappointing results resilient to extensive efforts to improve the efficacy of immunotherapy against cancer, patients and scientists are witnessing a revolution. A rapid translation of concepts from the bench to the bedside is finally making a difference in overall survival of patients with different types of cancers, including those traditionally considered non-responsive to immunotherapy. Clinical studies have proven unequivocally the effectiveness of T cell-based therapies that can induce regression of late stage cancers otherwise resistant to standard therapy. Regressions are associated with prolonged patients' survival, achieving, in some cases, durable disease-free survival.

Many written accounts on large studies that validate the clinical usefulness of immunotherapy have appeared monthly in high-impact journals. This is leading to a rapid inflation of the field characterized by the rapid expansion of tumor immunotherapy clinical programs and participation of oncologists to meetings focused on this discipline. In the last 3 years, for instance, the Society for Immunotherapy of Cancer (SITC) has more than doubled participation to its annual meeting with nearly 2000 attendees.

This long-awaited success is giving both clinicians and scientists new opportunities. The high frequency of objective responses allows for a more efficient study of mechanisms of responsiveness and identification of biomarkers as a smaller number of patients must be accrued to observe a sufficient number of responding cases. The shortened length of time necessary to perform informative clinical studies expedites the feedback loop stimulating research based on clinical evidence while simultaneously helping the design of second-generation clinical studies. In addition, the expansion of clinical protocols to larger patients cohorts in phase three or even post-licensing studies allows for a less fragmented approach to the understanding of human cancer biology by evaluating more homogenous patient populations in better controlled settings. This provides grounds for prospective validation of concepts developed during monitoring of early phase trials.

The clinical success has led to unprecedented nimbleness of regulatory agencies in approving novel therapeutics. This, in turn, has allowed a more flexible off-label use of therapeutics in combination. Combination therapy trials demonstrated that

the therapeutic potential of immunotherapy agents is complementary and not overlapping. Thus, the tremendous success of combining conceptually similar approaches such as anti-CTLA-4 with anti-PD1/PD1L as checkpoint inhibitor agents, which have shown synergistic enhancement of unleash T cell activation. Considering the central role that checkpoint inhibitors are taking in the treatment of several cancers, their relatively limited toxicity, and simplicity of administration, it can be anticipated that future combinatorial approaches will be centered around the addition of other therapeutics such as pathway inhibitors, anti-cancer vaccines, agonistic antibodies, cytokines, adoptive cellular therapies, anti-angiogenesis agents, chemotherapy, epigenetic therapy, and radiotherapy to checkpoint inhibitors. In particular, radiotherapy is taking a novel role in the treatment of cancer as a facilitator of anti-cancer immune effects through the demonstration of its abscopal effects: concurrent not-irradiated tumors regress in the presence of checkpoint inhibitor therapy after radiation. The abscopal effect is revolutionizing our understanding of the role played by radiation in modulating the biology of human cancers.

Several new concepts have also emerged throughout the implementation of clinical trials: a salient one is derived by the observation that, contrary to other anticancer therapies, responses to immunotherapeutic agents are of long duration and linked to long-term survival. It has also become clear that immune responses follow a distinct dynamic pattern diverging from that of classical responses to standard chemotherapy. The latter is characterized, when successful, by immediate although often ephemeral reduction in tumor burden. Tumors that respond to immunotherapy often increase in size before a reduction can be observed. This phenomenon is believed to be due to the inflammatory process induced by immunotherapy that leads to recruitment of immune cells within the tumor microenvironment. Another pattern peculiar to immunotherapy is the observation that several patients seem to benefit from long-term stable disease although the biology of this "halting" of tumor growth is currently poorly understood.

Challenges remain. The cost of immunotherapy treatments is quite significant. Therefore, several therapies are not readily available to all potential beneficiaries. Interestingly, a cost-effectiveness analysis of these treatments is not, to our knowledge, reported. Although the price for the individual treatment may be costly, its effectiveness, short duration, and limited toxicity may mitigate the overall cost of care compared to traditional approaches.

The optimal way to simultaneously avoid unnecessary exposure of patients to ineffective therapies while relieving the society from wasteful spending would be to predict a priori likelihood of response. The identification of predictive biomarkers will, therefore, take a leading role in the next future. We and others have shown that the functional orientation of immune cells toward a Th1 polarization is a harbinger of likelihood or response. Interestingly, the same functional orientation has been associated with good prognostic connotation in most cancers. Lack of immune activation is likely to correspond to resistance to immunotherapy, while the presence of a Th1-polarized immune phenotype may indicate a microenvironment preconditioned to respond. Immunotherapy further enhances the otherwise lingering immune response leading to a full-blown activation of an acute inflammatory

process similar to that observed during acute flares of autoimmunity or during acute transplant rejection. We referred to this phenomenon as "the Immunologic Constant of Rejection." An intermediate condition occurs when the same Th1 polarization is observed in association with improved prognosis. In that case, the immune response is not sufficient to completely eradicate the growth of cancer but can slow its progression. These observations will need further validation in the future before such signatures could be used for patient selection. A comprehensive discussion about the revolutionary role played by signatures of Th1 polarization in reshaping cancer staging or prediction of its responsiveness to therapy is beyond the scope of this volume. However, these findings clearly emphasize the central role played by T cells in controlling tumor growth.

Another limitation to the broad utilization of immunotherapy is the resistance to treatment peculiar to some cancer types. While novel immune therapeutics have greatly increased the range of immunotherapy expanding its proven efficacy to cancers previously judged to be immune-resistant, several cancers such as breast cancer remain quite unresponsive. Further work will need to be done to understand how ontogeny, together with genetic background of the host and somatic alterations, may affect immune responsiveness.

Thus, in conclusion, the progress of immunotherapy has been exponential and the unprecedented clinical outcomes are promising for the years to come. However, several challenges remain. Moreover, as the mechanism leading to tumor rejection has not been fully investigated nor completely understood using integrated system biology approaches, a better understanding will likely lead to further outcomes improvement.

This volume illustrates salient aspects of cancer biology relevant to the successful implementation of immunotherapy. Coverage includes the enhancement of antigen-specific immune responses by anti-cancer vaccines, modulation of the function of T cells within the tumor microenvironment, and the effect of genetic, epigenetic, developmental, and environmental determinants on T cell function. Also covered is the ex vivo expansion of T or other immune cells and their genetic modification or reprogramming to increase their ability to survive and expand when adoptively transferred back to the patients. Specific attention is devoted to the genetic manipulation of T cells through the introduction of re-directed T cell receptors, chimeric antibody receptors, and other genetic manipulation aimed at improving the effectiveness of anti-cancer agents. Furthermore, the revolutionary role of checkpoint inhibitors and their potential in combination with other immunotherapeutic approaches or with standard chemo and radiation therapy is extensively discussed.

We hope that the readers will find this volume useful and we would like to conclude with the famous quote from Winston Churchill: "This is not the end, it is not even the beginning of the end but, perhaps it is the end of the beginning".

Bethesda, MD, USA — Ena Wang
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Chapter 1
Insights on Peptide Vaccines in Cancer Immunotherapy

Kwong Y. Tsang, Caroline Jochems, and Jeffrey Schlom

Abstract Human tumor-associated antigens are generally weakly immunogenic and therefore able to escape detection by the immune system. Numerous studies have shown, however, that immune cells infiltrate many tumors, and that these cells are vital for keeping tumor burden in check. Immunotherapy can enhance this process by further stimulating tumor-recognizing cells while decreasing the function of immunosuppressive cells, such as regulatory T cells and myeloid-derived suppressor cells, thereby creating a more immune-activating tumor microenvironment.

Peptide vaccines can stimulate and activate T cells specific to tumor-associated antigens. Because peptides endogenously expressed by tumor cells are often weak immunogens, researchers are investigating various strategies for making them more immunogenic and more potent as vaccines. Here we review multiple strategies for enhancing peptide immunogenicity, including (a) peptides with amino acid substitutions at anchor residues and heteroclitic analogs, (b) multiple variance long peptides, (c) whole protein and 15-mer overlapping peptides, (d) multiple peptides recognizing different tumor-associated antigens, (e) class I and II epitope hybrid vaccines, (f) peptide-pulsed dendritic cells, and (g) combining peptide vaccines with other therapies. While it is unlikely that peptide vaccines alone could significantly affect progressive disease, the combination of these vaccines with the right adjuvants and/or immunomodulatory agents has shown promising results in clinical trials.

Keywords Peptide cancer vaccines • Immunotherapy • Combination therapy • Cytokines • Prime-boost regimen • Checkpoint inhibitors

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Introduction

Immune editing is an extrinsic mechanism of cancer suppression that initiates only after cellular transformation has occurred and intrinsic mechanisms of cancer suppression have failed [1]. The process of immune editing occurs in three phases: elimination, equilibrium, and escape. In the elimination phase, innate and adaptive immunity join forces to eliminate cancer cells before they become clinically apparent, rendering the host virtually cancer-free. In the equilibrium phase, cancer cells not eliminated in the elimination phase are prevented from proliferating by host immunity, which maintains the cancer cells in a state of functional dormancy. Equilibrium is a function of adaptive immunity, which may restrain cancer cell growth in the host for a lifetime. In the escape phase, cancer cells once held in equilibrium may escape recognition by adaptive immunity due to insensitivity to immune effector mechanisms and induction of immune suppression in the tumor microenvironment. Cancer cells that escape immune recognition proliferate and become clinically apparent. Therapies such as peptide vaccines have the potential to keep cancer cells in the elimination and/or equilibrium phase.

This review describes studies employing peptide-based cancer vaccines and prospects for improving their efficacy through the use of peptides with amino acid substitutions at anchor residues and heteroclitic analogs, multiple variance long peptides, whole protein and 15-mer overlapping peptides, multiple peptide epitopes from different tumor-associated antigens (TAAs), class I and II hybrid peptide vaccines, peptide-pulsed dendritic cells (DCs), adjuvants including toll-like receptor (TLR) agonists and cytokines, and combinations of peptide vaccines with various other therapies.

Peptide vaccines have several advantages over other cancer vaccine approaches. Short peptides (9 or 10 amino acid residues) that bind to major histocompatibility complex (MHC) class I molecules can induce specific $CD8^+$ T-cell responses that can lyse tumor cells expressing the cognate MHC class I and peptide [2, 3]. The quality of the immune response depends on the peptides and adjuvants used in the vaccine. Immune response rates approaching 100 % have been reported in some cases using multipeptide melanoma vaccines [4–6]. A mixture of a dozen peptides restricted to human leukocyte antigen (HLA)-A1, -A2, -A3, -A11, and -A24 can be a stable platform for a vaccine that can be used in 85 % of cancer patients, thus overcoming the limitation of peptide restriction. It has been demonstrated that this type of peptide mixture can induce immune responses in vaccinated patients with no negative effects from antigenic competition among the peptides in the mixture [4, 7, 8]. Other advantages of peptide vaccines include low production costs, stability, safety, their use as an off-the-shelf reagent, and their effectiveness as booster vaccines. On the other hand, peptide vaccines have some considerable limitations. In vivo, when a peptide vaccine is delivered into subcutaneous (s.c.) tissue, short peptides may bind to MHC on nonprofessional antigen-presenting cells (APCs) without optimal costimulation, which may induce tolerance. In addition, peptides in human plasma are rapidly degraded by exopeptidases and endopeptidases, and have a short half-life. In vaccinated patients, short peptides have no tertiary structure and thus may rapidly degrade before they can reach APCs. For example, the estimated half-life of MelanA/MART-1 peptide in fresh human plasma is about 22 s [9]. These issues can be overcome by

combining the peptide with the proper adjuvant, which may not only emulsify it for better delivery, but also increase the half-life and stimulate the immune system more efficiently to avoid possible induction of tolerance.

There are numerous TAAs being used as vaccine targets. Below is a description of TAAs employed in vaccines developed at the National Cancer Institute.

Tumor-Associated Antigens

Carcinoembryonic Antigen

Carcinoembryonic antigen (CEA; CD66) is a 180-kDa immunoglobulin-like oncofetal glycoprotein that is expressed on the cell surface of normal colonic mucosa and primarily functions in cellular adhesion [10]. CEA is also commonly overexpressed on adenocarcinomas arising from the breast, cervix, lung, and gastrointestinal tract [11, 12].

Mucin 1

Mucin 1 (MUC1; CD227) is a large transmembrane glycoprotein normally expressed at the apical surface of glandular epithelial cells [13]. In adenocarcinomas (i.e., breast, prostate, colorectal, ovarian, lung, bladder, and pancreatic) it is overexpressed and aberrantly glycosylated [14, 15]. Loss of epithelial-cell polarization also results in MUC1 expression throughout the cell surface. These characteristics make MUC1 a potential target for immunotherapy [16]. MUC1 is also expressed in hematologic malignancies such as B-cell lymphoma, chronic myelogenous leukemia, and multiple myeloma [17–19]. The N-terminal (MUC1-N) is the large extracellular domain that consists of a variable number of tandem repeats (VNTR) region and a non-VNTR region. MUC1-N is shed from cells, is present in the circulation of patients with advanced cancer, and is used as a tumor marker (CA15.3) in breast cancer patients [20]. The C-terminal of MUC1 (MUC1-C) has been shown by several groups to be extremely important in the initiation and progression of a range of human neoplasms [21–23]. Overexpression of MUC1-C makes it possible for malignant cells of epithelial or hematopoietic origin to exploit the physiologic stress response, and thus stimulate their expansion and survival [24].

Prostate-Specific Antigen

Prostate-specific antigen (PSA) is a 34-kDa glycoprotein that is expressed in normal prostate tissue and prostate cancer [25]. PSA is also expressed at very low levels in the paraurethral and perianal glands, placenta, breast (including breast cancer), and thyroid. However, except for breast cancer, these tissues do not secrete a significant

amount of PSA into the serum. Normally, PSA is secreted into the prostatic ducts. However, in prostate cancer the disordered glandular architecture causes increased amounts of PSA to diffuse into the serum, allowing PSA measurements to serve as screening and prognostic markers for prostate cancer. The immunogenicity of PSA has been demonstrated in multiple studies. Because PSA is secreted, it is not a good target for an antibody response. However, T cells can recognize any proteins made by cells once fragments of these proteins (peptides) are processed and presented on MHC molecules. It has been demonstrated that human cytotoxic T lymphocytes (CTLs) specific for PSA can be generated in vitro [26], and that some patients with advanced prostate cancer have naturally occurring PSA-specific T-cell responses [27]. Furthermore, Gulley et al. demonstrated that in patients with prostate cancer, a PSA vaccine could generate PSA-specific T cells that secrete interferon gamma (IFN-γ) and lyse PSA-expressing tumor cells in an MHC-restricted manner [28].

Brachyury

The transcription factor brachyury was initially identified as a molecule relevant to the formation of the mesoderm during murine embryonic development, which involves conversion of epithelial cells into mesenchymal cells [29]. Brachyury is thus a mediator of normal physiologic epithelial-mesenchymal transition (EMT) and metastasis. Subsequent studies revealed brachyury to be expressed in a range of human tumors, with limited levels in human adult testes and thyroid, and little or no expression in other normal adult tissues [30–33], making it an ideal target for cancer immunotherapy. Transcription factors such as brachyury, however, are generally believed to be difficult to target with small molecule targeted therapies due to their nuclear location and lack of a specific groove for the tight binding of a small molecule inhibitor [34]. An alternative approach to targeting transcription factors is vaccine-mediated T-cell therapy. Recent studies have identified an HLA-A2 class I brachyury peptide that is capable of inducing human $CD8^+$ CTLs in vitro [30]; these T cells were shown to be capable of selectively lysing a range of brachyury-expressing human carcinoma cell lines [30]. Two clinical trials are ongoing employing recombinant vectors expressing brachyury (NCT01519817 and NCT02179515).

Peptides/Proteins as TAAs

Many different TAAs have been used in cancer vaccines, either as the whole native protein, 9-mer peptide epitopes, 15-mer peptide epitopes, or after making changes in the endogenously expressed proteins in order to make them more immunogenic.