ADVANCED THERAPEUTICS
www.advtherap.com

Check for updates

Peptide Delivery Systems for Cancer Vaccines

*Xuedan He, Scott I. Abrams, and Jonathan F. Lovell**

Cancer vaccines aim to activate the immune system so it can seek and eradicate cancer cells. Peptide vaccines hold the minimalistic amount of biochemical information required for generating antigen-specific T cells to elicit anticancer responses. Unfortunately, results from most peptide cancer vaccine large clinical trials have been underwhelming. This may stem from a number of reasons, such as tumor-mediated immunosuppression, limited T cell-tumor infiltration, or insufficient T cell numbers induced in response to the vaccine. On their own, immunization with naked peptides usually does not induce a satisfactory response, so adjuvants and/or delivery systems are required. Beyond the traditional aluminum salts, oil emulsions, and carrier protein conjugates, next generation peptide delivery systems hold potential to induce stronger or broader responses that could eventually provide for improved immunotherapy outcomes. This review summarizes recent approaches to peptide cancer vaccines, in the context of emerging delivery systems.

1. Introduction

Cancer immunotherapy harnesses the immune system to fight the disease and has been an area of intense clinical and preclinical focus in recent years.[1,2] Checkpoint blockade inhibition using off the shelf monoclonal antibodies has generated excitement for cancer treatment and can activate endogenous pre-existing T cell responses.[3] Cancer vaccines act to expand pre-existing, as well as to induce de novo antitumor T cell responses, and are relatively early in the clinical translation process. For both immune checkpoint block and cancer vaccine strategies, the potency of endogenous immune activation is tempered by the immune suppressive tumor microenvironment. Therefore, it is now widely appreciated that optimal use of such immunotherapies must consider the incorporation of other conventional or experimental approaches that abrogate immune suppression.

Cancer vaccines hold particular promise for personalized cancer immunotherapy.[4] The vast majority of research in cancer vaccines aims for cell-mediated responses, but antibody-based cancer vaccines have also been investigated. For targeting the induction of T cell responses against class I or class II MHC-derived epitopes, common vaccine practices include the use of synthetic peptides, RNA, DNA plasmids, tumor lysates, viral vectors, engineered bacterial strains, or antigen-loaded dendritic cell (DC) vaccines.[5–10] These all have varying strengths and limitations.[11]

Peptide vaccines offer some advantages over other approaches. First, since Merrifield's 1984 Nobel Prize–winning innovation of solid phase peptide synthesis, peptide production, and purification has been continuously improved and automated so that high-quality, well-characterized, and inexpensive synthetic peptides are currently available at both research and clinical grade from a wide number of contract manufacturing organizations. Thus, peptides are easier and less expensive to synthesize and scale than whole proteins or most other types of antigens. Owing to their ease of synthesis, peptide vaccines can be tailor-made to any antigen target, without concerns about proper protein folding or whether the target antigen is intracellular or surface-bound. CAR T therapy must target surface antigens. Second, peptides represent the minimal and most essential biochemical information that comprises a cancer epitope. In this way, peptide vaccines can be used to develop vaccine approaches with well-understood mechanisms of actions. Immune responses can be exquisitely directed toward target epitopes. This is in contrast to vaccines such as tumor lysates, for example, which contain a multitude of antigens, other proteins, and additional tumor factors that render content characterization difficult or impossible. Third, since they can be produced in a modular fashion, multiple peptide epitopes can be combined for use in multivalent peptide vaccines.

Peptide vaccines carry some limitations. In many cases, the selection of immunogenic peptides depends on MHC binding algorithms, which may not be optimally effective. Second, because of the heterogeneity of MHC restriction in the human population, most peptide vaccines focus on the most prevalent MHC alleles. Peptide vaccines require expression of MHC class I molecules, which can be downregulated by many tumor types. However, perhaps the greatest limitation of peptide vaccines reflects their limited immunogenicity. On their own, peptides are usually insufficient to trigger satisfactory immune responses so they are combined with adjuvants and/or delivery systems. Such systems are an active area of research but still require more improvement. This review summarizes recent approaches in peptide delivery systems for cancer immunotherapy.

X. He, Prof. J. F. Lovell
University at Buffalo
State University of New York
Buffalo, NY 14260, USA
E-mail: jflovell@buffalo.edu
Prof. S. I. Abrams
Roswell Park Comprehensive Cancer Center
Department of Immunology
Buffalo, NY 14263, USA

The ORCID identification number(s) for the author(s) of this article can be found under https://doi.org/10.1002/adtp.201800060

DOI: 10.1002/adtp.201800060

© 2018 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim

1.1. The Immune-Suppressive Microenvironment

The immune system has numerous mechanisms in place to detect and eliminate cancer.[12] However, in turn, cancer can evolve numerous mechanisms to escape immune recognition or attack, some of which operate simultaneously.[13,14] Tumor-secreted factors, such as vascular endothelial growth factor (VEGF), transforming growth factor-β (TFG-β), prostaglandins, interleukin-10, and interleukin-6 can directly interfere with the function and differentiation of immune cells such as dendritic cells (DCs).[15] Tumor cells can downregulate or mutate MHC class I molecules, reducing tumor antigen display to engage $CD8^+$ T cells.[16,17] Alternatively, tumor cells can upregulate surface ligands, such as PD-L1 to mediate T cell exhaustion.[18] Moreover, several types of immune cells, such as regulatory T cells, myeloid-derived suppressor cells (MDSCs), and tumor-associated macrophages (TAMs) are recruited to tumors, and inhibit antitumor immune mechanisms.[19]

1.2. Cell Therapies

Adoptive cell transfer harnesses the patient's own immune cells such as tumor-infiltrating lymphocytes (TILs) or host cells that have been genetically engineered with antitumor T cell receptors (TCRs) or chimeric antigen receptor-expressing T cells (CAR T).[20,21] In CAR T cell therapy, T cells derived from blood are manipulated to express chimeric antigen receptors which target tumor-associated antigens (TAAs). These are then expanded and reinfused to patients to destroy antigen-bearing tumor cells. In 2017, two CAR T cell therapies which target CD19 (found on B cells) were approved by the US Food and Drug Administration (FDA); tisagenlecleucel (Kymriah), for the treatment of patients up to 25 years of age with B cell precursor acute lymphoblastic leukemia;[22] and Axicabtagene ciloleucel (Yescarta) for adults with diffuse large B cell lymphoma.[23] CAR T therapy has generated immense interest and investment from the pharmaceutical industry, although it still needs to be developed and validated for more common tumor types, particularly solid malignancies.[24]

1.3. Immune Checkpoint Blockade

Immune checkpoint pathways can be manipulated by cancers to avoid destruction by the immune system. If these inhibitory pathways are blocked by monoclonal antibodies, immune function can be restored to mediate antitumor activity.[25] In 1996, Allison and colleagues demonstrated that CTLA-4 blockade can combat tumors in mice.[26] In 2011, the FDA approved an anti-CTLA-4 monoclonal antibody (ipilimumab) for the treatment of metastatic melanoma.[27] In 2002, Chen et al. reported tumor regression in mice by blocking the PD-1/PD-L1 pathway, also by employing monoclonal antibodies that target that axis.[28] The FDA recently approved the use of anti-PD-1 antibodies, nivolumab (Opdivo), and pembrolizumab (Keytruda), based on promising clinical trial results, establishing checkpoint blockade as a new and additional form of immunotherapy against certain types of malignancies.

Xuedan He graduated with a master's degree in Nanochemistry and Nanomaterials from the University of Madeira, in Portugal. She is currently a Ph.D. student in biomedical engineering at the State University of New York at Buffalo. Her doctoral studies are focused on developing new approaches to peptide cancer vaccines.

Scott Abrams is a professor of oncology in the Department of Immunology at Roswell Park Comprehensive Cancer Center in Buffalo, NY. He also holds a joint appointment on the graduate faculty at the State University of New York at Buffalo. He received his Ph.D. in microbiology and immunology at Indiana University School of Medicine and carried out postdoctoral research at Washington University in St. Louis, followed by a senior staff fellowship and then appointment to principal investigator at the National Cancer Institute. Dr. Abrams' longstanding research focus is in tumor immunology.

Jonathan Lovell is an associate professor of biomedical engineering at the State University of New York at Buffalo. He obtained his Ph.D. degree from University of Toronto at the Institute of Biomaterials and Biomedical Engineering. Dr. Lovell's current research includes developing new approaches to nanoscale delivery systems, including for applications using peptides.

1.4. Cancer Vaccines

Cancer vaccines aim to induce the immune system to recognize and destroy malignant cells. Vaccines can prevent certain cancers from developing. Two antiviral prophylactic vaccines approved by the FDA have strong implications for cancer prevention. The human papillomavirus (HPV) vaccine has been shown to prevent cervical cancer and the Hepatitis B virus (HBV) vaccine can prevent hepatic cancer.[29] Therapeutic vaccines are given to patients diagnosed with cancer to direct a pre-existing or de novo-induced immune response against the disease. There is much clinical activity ongoing in developing effective therapeutic cancer vaccines.[30] Sipuleucel-T (Provenge) was the first therapeutic vaccine approved by the FDA for men with metastatic prostate cancer in 2010. This vaccine involves harvesting DCs from the patient, loading them with specific antigens, and reintroducing the DCs into the patient for the induction of the anticancer response.[31]

© 2018 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim