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Peptide Vaccines in Cancer Immunotherapy

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Abstract:

Traditional cancer treatment is based on surgery, supplemented by chemotherapy and radiotherapy. In recent years, new treatment options, such as targeted therapy, have gradually entered the clinic. However, for some patients who are inoperable or have metastasized, there are currently no sufficiently effective therapies to support long-term survival. Peptide vaccines are autoimmune system-based therapies that typically target the uptake of tumor antigens by antigen-presenting cells (APCs). Current clinical trials of peptide vaccines primarily target tumor-associated or tumor-specific antigens (TAAs or TSAs) and can be classified into two types: synthetic peptide vaccines and peptide vaccines derived from whole tumor cells. Although the peptide vaccines that have been reported are promising, the tumor microenvironment (TME) is a significant obstacle to the effectiveness of cancer immunotherapy. Using peptide vaccines as a future treatment for inoperable tumors, surgical follow-up, and as a complement to other treatments such as immune checkpoint inhibitors, tyrosine kinase inhibitors, chemotherapy, and radiotherapy is a possibility. This study aims to examine the various types and clinical applications of peptide-based therapeutic vaccines, which may offer significant insights into the current and future development of these vaccines.

Keywords: Peptide vaccine, tumor antigens, cancer immunotherapy, combination therapy.

1. Introduction

Theoretically, the patient's immune system can gradually recognize and kill tumor cells through a series of immune responses, also known as the cancer-immunity cycle [1]. However, Tumor cells have many strategies to evade immune surveillance, leading to tumor immune evasion [2]. Therefore, treatments that enhance patient immunity to control malignancies have been developed. Cancer immunotherapies are a rapidly expanding field in cancer treatment that boosts patients' immune functions to attack cancer cells at all stages of the immune system's role in the tumor life cycle, from prevention to treatment response [3]. Among them, peptide-based therapeutic vaccines are one type of cancer immunotherapy strategy.

Gaining knowledge of the cancer-immunity cycle can facilitate the comprehension of the mechanisms behind peptide-based therapeutic vaccines. Following the demise of immunogenic or necrotic cells, certain cancer antigens are released, including components discharged by dying tumor cells. Subsequently, by displaying the captured antigens on major histocompatibility complex (MHC) I and II molecules to T cells, dendritic cells (DCs) and other antigen-presenting cells (APCs) attract and stimulate effector T cells (Teffs). Afterward, the stimulated Teffs can mount a response against the antigens that are particular to malignancy. Finally, the activated T-effector cells are transferred and penetrate the tumor site in order to eliminate the cancerous cells. T cells specifically identify target tumor cells by means of the T cell receptor and trigger their programmed cell death (apoptosis) upon binding to them. The particular antigens present in the deceased tumor cells are subsequently released and collected by DCs, initiating a fresh cycle. This ostensibly seamless circulation mechanism may, in fact, give rise to several "incidents". For instance, it is possible that cancer-specific antigens evade detection or that activated T lymphocytes fail to be recruited to the relevant tumor tissue [1]. Thus, therapeutic vaccines ought to be formulated with the aim of augmenting the stimulation of immune responses while concurrently mitigating the impact of immunological checkpoints and inhibitors so as to optimize their potency and efficiency.

Therapeutic peptide-based vaccines currently use multiple epitopes, ranging from 5-30 amino acids in length, derived from either tumor-associated antigens (TAAs) or tumor-specific antigens (TSAs). These vaccines are specifically designed to stimulate and activate T cells that are specific to the peptides, thereby generating a continuous flow of immune responses against cancer cells [4]. Pep-

tide-based cancer vaccines are often designed to focus on the antigen presentation stage. This means that the vaccine can consist of either peptides extracted from a protein uniquely produced by the tumor or peptides obtained from entire tumor cells that are rich in antigens.

About thirty years after Plaen et al. found the first neoantigens recognized by T cells, Khodadoust et al. highlighted in March 2017 that antigenic epitopes can bind with MHCII neoantigens, resulting in the formation of MHCII-antigen peptide complexes. These complexes are subsequently identified by immune cells, leading to the activation of immune responses [5]. Four months later, Professor Catherine J. Wu developed a peptide vaccine targeting neoantigens, which effectively treated melanoma [6]. Since then, the application of epitopes from TAAs and TSAs in peptide vaccines is increasingly being studied and reported.

Clinical trials are currently underway for two therapeutic peptide vaccines against human papillomavirus (HPV): the four-truncated HPV16 E6 peptide vaccine and the HPV E6-E7 overlapping peptide vaccine. Both vaccines have exhibited favorable performance in eliciting specific cellular immune responses [7, 8]. CIMAvax-EGF, a peptide vaccine approved in Cuba for non-small cell lung cancer (NSCLC), has demonstrated good safety and effectiveness [9]. As one of the cancer immunotherapies, peptide vaccines have obvious advantages, including high specificity, small side effects, easy control, good stability, potential for long-term immune memory, and high cost-efficiency compared with other therapies [10-12]. Most notably, in comparison to the complete length of antigens, peptides exhibit a reduced propensity to elicit allergic or autoimmune responses [13]. Immunosuppression occurring in the tumor microenvironment (TME) is often considered to suppress the antitumor response [14]. Therefore, the future design of peptide-based vaccines in cancer immunotherapy may need to move in the direction of addressing this conundrum.

This review aims to examine the various types and clinical applications of peptide-based therapeutic vaccines, which may offer significant insights into the current and future development of these vaccines.

2. Tumor Antigens

Current peptide-based vaccines rely primarily on peptides derived from TAAs or TSAs. As of now, the majority of cancer therapeutic vaccines employ TAAs as the primary targets. TAAs are self-proteins characterized by abnormal overexpression in cancer cells, although they may also be partially expressed in normal tissues [15]. TAAs comprise three distinct categories of antigens: cancer/germline antigens, such as MAGE-A1, which are typically expressed exclusively in germline cells endowed with immune privileges [15, 16]; cell lineage differentiation antigens, including tyrosinase, which are typically absent in adult tissue [17]; and antigens that are excessively expressed in cancer cells, including HER2 or neoantigens of mutation-derived epitopes [18]. Compared to the TSAs, a larger number of targets have been identified. Some TAAs have undergone extensive preclinical and clinical research for peptide vaccines. These TAAs, which include Survivin, TTK protein kinase (TTK), carcinoembryonic antigen (CEA), mucin (MUC), and vascular endothelial growth factor receptor (VEGFR), have limited self-tolerance and high immunogenicity [19]. Using TAAs as targets in the development of peptide vaccines presents two significant challenges: the inadequate enhancement effect induced by stimulating Teffs and the infliction of harm upon healthy cells [15]. To prevent autoimmune reactions, it is highly probable that the body lacks intrinsic B cells and T cells that can robustly recognize TAAs; therefore, cancer vaccines must augment the immune attack against cancer cells by stimulating residual low-affinity TAAs. However, despite the utilization of potent adjuvants, co-stimulators, and other substances in an effort to enhance the activation and amplification of TAA-specific T cells, the efficacy of cancer vaccines may remain limited. For example, PROSTVAC-VF, a prostate cancer metastatic vaccine, induces the proliferation of antigen-specific T cells via epitopes derived from prostate-specific antigen (PSA), which is classified as a cell lineage differentiation antigen. Due to the lack of statistically significant differences in PSA-specific T cell levels in peripheral blood before and after vaccination, Phase III was terminated as it proved to be futile [20, 21]. Moreover, even if TAAs are poorly expressed in normal cells, a strong attack of Teffs on normal cells carrying the corresponding TAAs may cause some degree of collateral damage. In studies utilizing chimeric antigen receptor-engineered T cell therapy (CAR-T), off-target toxicity has been identified; however, this issue appears to be amenable to resolution. As an illustration, killer inhibitory receptors (KIR), such as PD-1-based inhibitory anti-CD19 CAR-T, can prevent the annihilation of healthy cells by virtue of an additional KIR receptor capable of normal cell recognition [22]. Peptide-based vaccines may potentially overcome off-target toxicity at tumor sites through the development of multi-site complex peptides. TSAs are divided into three main groups based on their origin: oncoviral antigens, shared neoantigens, and private neoantigens [15]. Oncoviral antigens are frequently selected as prophylactic antiviral vaccine targets due to their high immunogenicity. Additionally, certain targets have been

identified for therapeutic peptide-based vaccines, including peptide segments derived from the E6 and E7 proteins of HPV [7, 8]. However, the selection of viral oncoprotein targets is generally restricted due to the scarcity of cancer-related viruses, which primarily consist of hepatitis B virus, hepatitis C virus, and HPV. Neoantigens, which possess tumor-specificity similar to viral oncoproteins and are recently identified antigens produced by cancer-specific mutations, have been regarded for quite some time as the optimal target of antitumor immune responses [6]. In clinical settings, the initial step often involves conducting genome sequencing on tumor tissues to identify mutations specific to individual patients. Subsequently, these mutations can be compared with existing neoantigen vaccines. In cases where off-the-shelf neoantigen vaccines are not readily available, the option of developing a custom-made private neoantigen vaccine may be considered. To increase economic benefits, a private neoantigen vaccine can be manufactured by assembling multiple epitopes. It has been demonstrated that an immunogenic private neoantigen vaccine containing twenty predicted personal tumor neoantigens is safe and efficacious for the treatment of melanoma patients [6].

The researchers employ machine learning techniques to accurately forecast mutant peptides that exhibit a high binding affinity for autologous human leukocyte antigen (HLA) molecules. This capability enables the potential to create personalized neoantigens for a wide range of malignancies. By employing this approach, scientists are able to conduct further, more comprehensive experiments and developments in an effort to simplify and minimize the complexity and expense of tailored neoantigen vaccines.

3. The Application of Peptide Vaccine in Cancer Treatment

While peptide vaccines have shown promise in inducing specific T-cell immune responses against tumors, their efficacy as monotherapy remains relatively low. In a clinical trial, randomly allocated individuals with TERT-expressing and HLA-A*201-positive NSCLC were given either Vx-001 or a sugar pill. Only 29.2% of those who received the vaccine had lasting TERT-specific immune responses, which is a low level of effectiveness [24]. Therefore, due to the poor efficacy of peptide vaccines alone, researchers have begun to explore peptide vaccine combination therapies. These combinations may include adjuvants [25], agonists [26], immune checkpoint inhibitors [27], and tyrosine kinase inhibitors [28, 29] to enhance the overall effectiveness of the treatment.

In a clinical trial, 22 patients who had previously undergone radical prostatectomy were vaccinated with a synthetic long-peptide vaccine targeting RhoC with the adjuvant Montanide ISA-51. The vaccine successfully induced effective CD4 T cell immunity in most patients and lasted for at least ten months [25]. Like adjuvants, Castro et al. found that DCs become significantly more active when they combined the STING agonist c-di-AMP (K3/c-di-AMP combo) with the TLR9 agonist K-type CpG oligodeoxynucleotides (K3 CpG) [26]. In addition, combination therapy with immune checkpoint inhibitors and tyrosine kinase inhibitors has shown more promising therapeutic efficacy. In order to identify tumor mutations in 82 patients (including those with melanoma, NSCLC, and bladder cancer), Ott et al. utilized bioinformatics algorithms to select somatic mutations to generate neoepitopes of high quality. These neoepitopes were then incorporated into the personalized peptide vaccine, NEO-PV-01. The NEO-PV-01 vaccine comprises a blend of up to 20 epitopes tailored to the patient's specific mutated sites. It is administered in conjunction with the adjuvant poly-ICLC to enhance its effectiveness. Following this, nivolumab (a PD-1 inhibitor) was administered for an extended period following the vaccination and an additional 12 weeks prior to it. This clinical trial demonstrated that the therapy is feasible and safe, with no serious adverse events observed related to treatment. All 51 patients who completed the vaccination displayed neoantigen-specific CD4 and CD8 T cell responses. These vaccine-induced T cells demonstrated a cytotoxic phenotype, exhibited the ability to migrate to tumors, mediated cell killing, and generated long-lasting T cell responses. Moreover, the therapy triggered specific immune responses to neoantigen epitopes that were not part of the vaccine formulation. Despite lacking a control group administered with nivolumab alone, the data from this trial show favorable comparisons with historical data on anti-PD-1 monotherapy [27]. Furthermore, according to a Phase IIb controlled trial, triple-negative breast cancer patients benefited significantly more from the combination therapy of trastuzumab and the nelipepimut-S peptide vaccine compared to those treated with trastuzumab monotherapy [28]. Nevertheless, research has indicated that trastuzumab induces immune evasion by upregulating tumor PD-L1, whereas anti-PD-1 and trastuzumab combination therapy may bolster the effectiveness of the peptide vaccine HER-Vaxx and thwart immune evasion [29]. Notably, many clinical trials preferred combining peptide vaccines with conventional treatment modalities to enhance patient survival due to the low efficacy of peptide vaccine treatment alone. Awad et al. presented the findings of a Phase Ib clinical trial that evaluated the effectiveness of a tailored neoantigen vaccine, NEO-PV-01, in combination with pemetrexed (an antifolate), carboplatin (a che-

motherapeutic drug), and pembrolizumab (a PD-1 inhibitor) as the initial treatment for advanced non-squamous NSCLC. This study revealed that a total of 38 participants did not experience any significant adverse effects linked to the medicine. The combination of peptide vaccine, chemotherapy, and anti-PD-1 treatment demonstrates strong efficacy, especially in relation to CD4 T cells [30]. A separate Phase II trial conducted on patients with inoperable stage III NSCLC showed that the administration of chemotherapy followed by immunotherapy using telemovie (a peptide vaccine) and bevacizumab (an anti-VEGF antibody) brought about a notable increase in overall survival. This improvement was observed with the application of monoclonal antibodies and peptide vaccines following chemotherapy or radiotherapy [31]. The H3K27M-vac is a peptide-based vaccine designed specifically for treating diffuse midline glioma. When combined with anti-PD-1 therapy, it induces long-term immune responses that target specific mutations in the majority of individuals. However, these responses gradually diminish over time [32]. The clinical research investigating the efficacy of H3K27M-vac, combined with atezolizumab (a PD-L1 inhibitor), is now in progress [33].

4. Limitations & Future Outlooks

Although peptide vaccines have shown minimal success in recent clinical investigations, researchers are persistently exploring strategies to augment their potency. The researchers discovered that peptide vaccination should be given when there is an optimal balance between T effector and target cells and when immune cells are moderately activated [4]. An analysis of 2,588 individuals diagnosed with cancer revealed that those who had a low count of neutrophils and a high count of lymphocytes in their blood prior to receiving a vaccine, along with low levels of pro-inflammatory cytokines, had a higher chance of surviving overall after peptide immunization [34]. Moreover, the level of T-cells that identify specific epitopes in the bloodstream is inadequate to prove the effectiveness of the peptide vaccine since immune responses of T lymphocytes in the TME have certain limits. Although there may be an adequate amount of Teffs present in the peripheral circulation, the magnitude and effectiveness of tumor-infiltrating T lymphocytes could not be sufficient to suppress tumor growth or eradicate tumors. While the exact quantity of antigen-specific T cells required for effectiveness is presently uncertain, it is recommended that the examination of patient tumor-infiltrating lymphocytes be used instead of solely detecting peripheral antigen-specific T cells to assess the efficiency of vaccinations [15].

Although peptide vaccines in combination with monotherapy have shown promising results, the contribution of peptide vaccines in this context is not necessarily outstanding. In a study comparing the effectiveness of MDX-010 monotherapy, melanoma vaccine monotherapy, and combination therapy in patients with HLA-A2*0201-positive melanoma, it was found that MDX-010 monotherapy was nearly as effective as the combination therapy. In contrast, melanoma vaccine monotherapy was notably less effective [35]. This highlights the need for a monotherapy control arm clinical trial validating the effectiveness of peptide vaccines. Solid tumors are currently the primary target of peptide vaccines in clinical trials, including melanoma. There is an urgent need for therapeutic vaccinations to treat malignancies that cannot be operated on. Upcoming clinical trials will increasingly focus on treating inoperable cancers like glioma and investigate novel possibilities for combining different medicines. When deciding on immune checkpoint inhibitors for combination therapy, it is advisable to prioritize picking immune checkpoint inhibitors that target the tumor side (such as PD-L1) rather than the T-cell side (such as PD-1). This is particularly important in order to minimize harm to healthy cells.

5. Summary

Despite the presence of two major challenges in developing peptide vaccines that utilize tumor-associated antigens (TAAs), TAAs have a wider range of expression in comparison to tumor-specific antigens (TSAs). As a result, most research has predominantly concentrated on TAAs as targets for peptide vaccines. TSAs, particularly neoantigens, should be increasingly prioritized, considering the possible adverse effects of TAAs. The synthetic peptide vaccine is likely to have fewer contaminants and higher efficacy compared to the tumor cell-derived peptide vaccination. Thus, the primary focus for future therapeutic applications will be on synthetic peptide vaccines targeting neoantigens. While the effectiveness of peptide vaccines is currently not very encouraging, they provide a new ray of hope for cancer patients who are unable to undergo surgery and can only receive palliative care. The integration of peptide vaccinations with other immunotherapies and conventional treatments has greatly enhanced patient survival, indicating the promise of peptide vaccines as a viable treatment option for cancer.

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