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New Development of Vaccine Technology in Tumor Therapy

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Abstract. Cancer vaccines are a crucial component of tumors immunotherapy, offering the advantage of minimizing adverse reactions to induce tumor regression. They also enable the establishment of lasting anti-tumor memory. Recent years have seen significant breakthroughs in cancer vaccines, including the customization of personalized vaccines and the transition from passive immunization to active treatment. Currently, most cancer vaccine future goals focus on improving cost and efficiency such as combining immunology and bioinformatics to predict more accurate vaccine epitopes. This paper focuses on three innovative technologies in therapeutic cancer vaccines: cell vaccine, peptide cancer vaccine and nucleic acid cancer vaccine. This paper summarizes new selection of antigen-presenting cells for autologous tumor cell vaccine and allogeneic tumor cell vaccine, new research on adjuvants of peptide cancer vaccines and new nucleic acid cancer vaccine delivery platform. In addition, the combination of therapeutic vaccines is briefly discussed. These new technologies offer cancer patients new treatment options and hope.

Keywords: immunotherapy, cancer vaccine, immunotherapy.

1. Introduction

Tumors refer to the abnormal growth of cells or tissues, which are usually divided into Benign Tumors and Malignant Tumors. Malignant tumors are called cancers. According to the American Cancer Society estimates that 2,001,140 new cancer cases and 611,720 cancer deaths are projected to occur in the United States in 2024 [1].Currently, traditional cancer therapies such as radiotherapy, surgery and chemotherapy may not necessarily be efficient and often cause significant suffering. However, new tumor immunotherapy has become a turning point in cancer treatment. It activates anti-tumor immune cells and enables the immune system to eliminate tumor cells based on the cancer immune cycle. Compared to traditional cancer therapies, immunotherapy can be widely used and has fewer side effects. However, some tumor immunotherapies have limitations. For instance, immune checkpoint inhibitor (ICI-DM) may induce diabetes [2], and chimeric antigen receptor cells (CAR) may lead to autoimmune toxicities resulting from specific T-cell infiltration of the heart. Among the most important technologies in cancer immunotherapy are cancer vaccines. Cancer vaccines can not only induce tumor regression without adverse effects, but also generate anti-tumor memory. Cancer vaccines are divided into preventive and therapeutic vaccines. Preventive vaccines protect against cancer by preventing or eliminating certain viral infections. For example, the cervical cancer vaccine prevents human papillomavirus (HPV) infection and prevents cervical cancer. Another example of a preventive vaccines is the hepatitis B vaccine (HBV). Therapeutic vaccines apply to cancers that have already occurred. By

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activating their own specific immune functions, it ought to help the body fight cancer cells. This article will focus on the new developments in three therapeutic cancer vaccines: cellular vaccine, peptide cancer vaccine and nucleic acid cancer vaccine. In addition, their challenges and opportunities are briefly discussed.

2. Overview of Cancer Vaccines

The origins of therapeutic cancer vaccines date back to the 18th century. American doctor Coley discovered that erysipelas toxin secreted by Streptococcus pyogenes could induce tumors regression in sarcoma patient. In the 20th century, researchers discovered antigens in autologous tumor cells or tumor cells lysates. While they tried to inject patients with lysates and developed the first cancer vaccine. Therapeutic cancer vaccines do contain cancer antigens that are typically specific proteins or peptides. When these antigens enter our body, they are recognized by the immune system firstly and captured by antigen presenting cells (APC), especially dendritic cells (DCs). After being processed into major histocompatibility complex (MHC) I/II, they are presented to the surface of T cells. T cells are then activated, with T helper cells (CD4+) assisting cytotoxic T lymphocytes (CTLs) (CD8+) in recognizing cancer cells with specific antigens. Once CTLs bind to cancer cells, they release cytotoxins to kill the cancer cells. Additionally, if tumor cells express MHC-II, CD4+T cells can directly release cytotoxicity. Therefore, cancer vaccines selectively target cancer cells without harming normal cells. Currently, the following cancer therapeutic vaccines have been developed that are famous ones. Sipuleucel-T (trade name: Provenge) is a therapeutic vaccine for prostate cancer developed by Dendreon (later acquired by Astrazeneca). The vaccine works by activating the patient's own immune system to attack the tumor. CIMAvax-EGF, a therapeutic vaccine developed in Cuba for the treatment of non-small cell lung cancer. Its clinical trials showed that patients who received the vaccine lived twice as long as those who did not, with 5-year survival rates soaring from 0% to 23%. Another example is mRNA-4157 (Personalized Cancer Vaccine), a personalized cancer vaccine jointly developed by Moderna and Merck for the treatment of high-risk melanoma. It can be used in combination with pabolizumab (Keytruda) to improve relapse-free survival in patients with high-risk melanoma. The combined group had a 44 % lower risk of cancer recurrence or death. The characteristics of these three therapeutic vaccines are summarized in Table 1.

Table 1. Examples of Clinical Cancer Therapeutic Vaccines.

Name	Development Company	Treatment type	Therapeutic effect
Sipuleucel-T	Dendreon	prostate cancer	activatethe immune system to attack the tumor
CIMAvax-EGF	A Company in Cuba	lung cancer	five-year survival rates have soared from 0% to 23%
mRNA-4157	Moderna and Merck	melanoma	the risk of cancer recurrence or death was reduced by 44 percent.

3. Cell Vaccine

Tumor cell vaccines are a critical component of therapeutic vaccine. These vaccines utilize tumor cells or tumor-associated antigens as immunogens. After processing into the patient's body, it can induce the body to produce specific cellular and humoral immune responses to attack tumor cells. This can inhibit the growth and spread of tumors in the human body. Currently, tumor cell vaccines are broadly categorized into autologous tumor cell vaccines and allogeneic tumor cell vaccines. Autologous tumor cells (ATC) are highly effective in activating tumor-reactive T cells[3]. Therefore, it can be used as a good tumor-associated antigen (TAA). Autologous tumor cell vaccine (ATV), prepared from the patient’s own tumor cells, offer high specificity and safety. Despite being a preferred choice for personalized immunotherapy, they do present certain challenges in clinical treatment.[3]. On the other hand, ATVs rely more on existing tumor cell lines as antigen sources and usually require the same

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preparation in the laboratory. So they also have the advantage of standardized production. However, due to individual patient differences, the efficacy of these vaccine can vary. Both types of vaccines often cooperate with DC cells the most potent APCs, discovered by Canadian scientist Ralph Steinman in 1973. DC vaccine is a widely used platform for cancer therapeutic vaccines [4].It is currently the most potent APC in the body and the initiator of the collective immune response. T cells activated by DC are able to recognize and kill tumor cells expressing TAA. At the same time, DC cells can also be isolated and cultured in the laboratory to carry tumor-related antigens, and then prepared into an independent vaccine to induce anti-tumor immune response in patients. Sipuleucel-T, developed by Than Shwe, is the world's first FDA-approved DC vaccine for the treatment of advanced metastatic prostate cancer. In recent years, somatic tumor cell vaccine and autologous DC vaccine are often compared in clinical studies. Researchers hope that ATV can make certain progress in other antigen-presenting cells or new technologies.

3.1. Autologous Tumor Cell Vaccine

At present, autologous tumor cell vaccines are gradually becoming a personalized immunotherapy. This technology has shown significantly effectiveness not only in eliciting anti-tumor immune response but also in preventing tumor recurrence and metastasis. However, ATVs are not clinically effective for all cancer patients, which may be due to several reasons. Primarily, because most ATVs rely on autologous dendritic cells, the treatment costs are higher and may be less effective. CTL activation requires large doses of ATV so that tumor antigens can be recognized quickly. If it is ATV alone, it is almost impossible for CTL to completely infiltrate the tumor matrix [5]. To address these issues, current advancements in autologous tumor cell vaccine technology focus on selecting new antigen-presenting cells as amplifiers and carriers, such as tumor infiltrating lymphocytes (TILs) and natural killer cells (NKs). Another approach is to find a way to quickly activate specific CTLs.Another approach is to find ways to quickly activate specific CTLs. Adoptive cell therapy, which uses in vitro activated autologous TILs and injects them into the patient via intravenous infusion, has proven to be effective. [6].Researchers have discovered that TILs harvested from tumor tissues possess complete signal transduction molecules, and when these in vitro cultured TILs are transfused into the bloodstream, they can successfully enter tumor tissues, thereby expanding the immune response. TILs therapy has shown a high rate of disease control. NK cell therapy, which is now being studied in depth. Because NK cells are the first line of defense of the immune system, they can directly detect and destroy infected and malignant cells. The researchers found ways to stimulate large amounts of CTLS with little or only ATV. It is the use of the following two adjuvants that can activate the T-effect response to inhibit tumor rejection. The two adjuvants are cytosine-phosphodiester-guanine oligodeoxynucleotide and granulocyte-macrophage colony-stimulating factor.

3.2. Allogeneic Tumor Cell Vaccine

As described above, an allogeneic tumor cell vaccine is made using a tumor cell line other than the patient's own after specific treatment. These cell lines often have an antigenic signature similar to the patient's tumor. For example, HS-110 (Viagenpumatucel-L), developed by Heat Biologics in the United States, is used to treat advanced lung cancer. The vaccine is made from a specific lung adenocarcinoma cell line that carries a typical adenocarcinoma cell high expression antigen. The current clinical evaluation of the safety and efficacy of HS-110 combined in the treatment of advanced lung adenocarcinoma shows that the combination therapy is very well. However, recurrence is still the main cause of treatment failure after allogeneic tumor cell vaccination. There's an HMEC natural cell surface antigen known as SANTAVAC (Set of All Natural Target Antigens for Vaccination Against Cancer), which is currently a relatively innovative use of antigen compositions for vaccination based on a set of specialized derivatives Alloantigen compositions can also be effectively used for anti-cancer vaccination [7]. This combination stimulates the immune system more effectively, producing a stronger memory effect and reducing the likelihood of relapse. Additionally, the tumor cell lines in the vaccine have lost their ability to proliferate, so they don't form new tumors in the body.

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4. Peptide Cancer Vaccines

Peptide cancer vaccines generally refer to the use of immunogenic polypeptide fragments as antigens. These vaccines stimulate the body's immune system to produce a specific immune response to treat or prevent cancer. Currently, the common antigens selected for peptide-based cancer vaccines are tumor-associated antigen (TAA) and tumor-specific antigen (TSA). These antigens are bound to MHC molecules by peptide fragments treated by APC and presented to CD8+ cytotoxic T cells. After T cells recognize and bind to these polypeptide-MHC complexes, they are activated and differentiate into effector T cells, which in turn attack tumor cells expressing the corresponding antigen This process is called active immunotherapy. In active immunotherapy, the host's immune system is reactivated or restimulated,producing an effective tumor-specific immune response and leading to tumor regression[8]. At present, peptide-based preventive cancer vaccines have been extensively developed, while therapeutic cancer vaccines have yet to be perfected. Peptide-based cancer vaccines are currently classified into several categories: long peptide cancer vaccines, personalized peptide-based cancer vaccines. And they all have their own creative and limiting aspects. An effective cancer vaccine can only be developed by considering all the different aspects.

4.1. Long Peptide Synthetic Peptide Cancer Vaccine

Long chain synthetic peptides (LSPS) are now well established for the synthesis of vaccines [9]. Long peptide vaccines refer to the use of longer peptide chains as antigens, which can more fully simulate the structure of natural antigens. This can enhance the recognition ability of the immune system. In current clinical application cases are in the treatment of melanoma, long peptide vaccines (such as Neo Vax) have shown good efficacy. By single-cell sequencing,it has been found that the long-term persistence of neoantigen-specific T cell responses demonstrates the effectiveness of long-peptide vaccines in inducing anti-tumor immunity. As long peptide and synthetic peptide vaccines, the most critical step after vaccination is antigen presentation. At present, the researches on cross-presentation of long peptides compared to short peptides is still in progress. Cross-presentation process refers to the presentation of exogenous Ag antigen peptides to MHC-I molecules by DC [10].Therefore, the cross-presentation is related to exogenous Ag. Two pathways of cytosolute and vacuole cross-presentation have been proposed. The cytosolic pathway refers to the entry of granular antigens into the phagocytosis of APC through phagocytosis or pinocytosis. The phagocyte rupturion makes its antigens to escape into the cytoplasm. This process may be mediated by specific receptors, such as DNGR-1 and may be related to irreparable damage to the membrane. The antigens that escape into the cytoplasm are then cleaved into small peptides of varying lengths by the proteasome. These small peptides are transported to the endoplasmic reticulum (ER) by Transporter Associated with Antigen Processing (TAP). The antigenic peptides then bind to the newly born MHC Class I molecules in the ER, where normal presentation occurs. The cytoplasmic pathway also involves the binding of foreign antigens to MHC Class I molecules via non-classical pathways in some cases. In the vacuole pathway, the entire process takes place in the vacuole. For example,the internal proteins are cleaved by endolysosomal peptidase and the resulting peptides are loaded onto MHC-I molecules. Therefore, this process does not require transmembrane transfer of Ag [11]. Although there is a new progress in the antigen presentation process of synthetic growth peptide vaccines, there is a poor immunogenicity. Vaccines containing target antigen-synthesizing peptides typically require additional immune stimulants and adjuvants to stimulates the corresponding immune response [11]. Recently researchers have found that the production of cancer cells can trigger the release of inflammatory cytokines and aggregation of immune cells. If this induces anti-tumor immunity, then the inflammatory response of tumor cells may potentially be a natural adjuvant. This could help the synthetic peptide vaccine induce an antigen-specific immune response. Therefore, the timing and dose of vaccination are also issues worthy of further discussion.

4.2. Personalized Peptidyl Cancer Vaccine

A personalized peptide-based vaccine is a peptide-based vaccine designed for an individual patient based on specific tumor antigen. The antigenic peptides in the vaccine are derived directly from the

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patient's own tumor cells making them precise and safe. At present, bioinformatics analysis techniques are mainly used to find specific antigenic peptides on the surface of tumor cells in patients. These antigenic peptides are then synthesized in the laboratory. Personalized peptide-based vaccines are prepared by mixing the synthesized antigen peptides with appropriate adjuvants such as GM-CSF, etc. Therefore, the biggest challenge for personalized peptide-based cancer vaccines is how to predict the epitope with the highest immunogenicity and reduce the cost. To address this, computational tools, including those for the rare HLA Class I and HLA Class II haplotypes, are being improved to predict affinity and stability for binding to HLA molecules. Other potential predictors of immunogenicity are also researched, such as sequence similarity to microbial HLA epitopes. These are key directions for optimizing vaccine target selection [12]. Although it is a personalized peptide vaccine, the amount of production is not the most critical factor for application in a commercial environment. Therefore, researchers reduce the expected delivery time of personalized peptide-based cancer vaccines to less than four weeks by standardizing production speed and manufacturing processes.

5. Nucleic Acid Cancer Vaccine

Nucleic acid cancer vaccines are a new type of vaccine based on modern biotechnology. They involve the direct introduction of foreign genes, such as DeoxyriboNucleic Acid(DNA) or Ribonucleic Acid (RNA), that encode antigen proteins into animal cells. These antigen proteins are synthesized by the host cells' expression system, thereby inducing the host to produce an immune response to the antigen protein. .Currently, nucleic acid cancer vaccines are mainly divided into DNA vaccines and RNA vaccines. DNA vaccines are also called naked vaccines because they do not require a chemical carrier. When a DNA vaccine enters the host, it is taken up by antigen-presenting cells and then expresses the pathogen's protein antigen inside the cell. The efficacy of RNA vaccines, especially mRNA vaccines, is very straightforward. mRNA vaccines carry mRNA sequences that encode antigen proteins. After entering the cell, these mRNA sequences directly the synthesis of proteins, which induces an immune response. Nucleic acid cancer vaccine are strong targeting and small side effects, which is considered to be a major breakthrough in the field of cancer therapeutic vaccines. At present, with the rise of nanotechnology and the continuous development of biotechnology, a new delivery platform for cancer nucleic acid vaccines is provided. And many new cancer nucleic acid vaccines are undergoing clinical trials. The mRNA-4157 (Personalized Cancer Vaccine) personalized cancer vaccine, developed jointly by Moderna and Merck, is a practical example.

5.1. DNA Vaccine

DNA vaccines offer not only personalized and specific treatment, but also a fast effective time. Compared with SLP, DC and RNA vaccines, multi-epitope vaccines in DNA plasmid form have higher yield, higher safety and more molecular flexibility [13]However, DNA vaccines also face certain challenges such as unstable DNA transfection ability. It is well known that DNA vaccine plasmids containing target antigen genes can be constructed in vaccines. However, these plasmids need to escape the lysosomal degradation. New technology to solve the DNA transfection problem can strengthen the delivery platform and change the delivery route. There is a new type of delivery platform: the natural DNA delivery platform using yeast. Yeasts are not only cheap and easy to obtain, but also have immune-stimulating properties. What is more, they can even act as adjuvants in vaccines themselves. Because of the natural structure of the yeast cell wall,even in oral conditions, DNA can escape digestion. Yeast cell walls contain β-glucans, but the stomach lacks enzymes that degrade them. Yeast is internalized in M cells and transported to the underlying Peyer's Patches domain. The APCs organelles then phagocytize the yeast, and the lysozyme metabolizes the yeast in vivo without degrading the others. The yeast then releases the DNA. The DNA is directed to the nucleus for transcription and released into the cytoplasm in the form of mRNA, which is translated in the ribosomes. The protein is processed in the proteasome and cut into peptides, which are presented to the cell surface through the MHC-I pathway . Then it can be presented to CD8+ T cells to activate cytotoxic reactions. So this platform ensure smooth transfection of DNA and stimulates immune defenses. Currently, most methods that change the delivery route

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include the use of intradermal (ID) and intramuscular (IM) electroporation technology. This method can stably transferred DNA into cells by electric current. In addition, there are particle-mediated epidermal delivery (PMED) and needle-free injection systems (NFIS) that may also replace traditional needle injection methods.

5.2. RNA Vaccine

Messenger RNA (mRNA)-based cancer vaccine has become a popular approach for developing personalized and effective antitumor immunotherapy [14]. mRNA vaccines are not only relatively simple to design and manufacture, but also can quickly express antigen proteins in cells. This allows for a rapid respond to new pathogens or cancer antigen mutations. mRNA is naturally degraded after completing its mission in the cell and has no long-term effects on the human body. However, the main limitation of mRNA vaccines is their instability in human body, which makes clinical treatment challenging. Therefore, our new technology to solve the problem of RNA stability can also start from the delivery platform. At present, nanotechnology is the mainstream in mRNA delivery. In this paper, dendritic cells are the main antigen presenting cells. It is also the primary target cell population in our body. In theory, the mRNA of the nanocarrier will be interlinked with the dendritic cell. The researchers studied in vitro vaccine screening systems for DC. They found that they could use the lipid-like material C1 with a 12-carbon tail as a delivery platform. It can successfully deliver mRNA to DC and induce T cell response [14]. After the identification of RNA vaccines nanomaterials, new advances have been made in the selection of tumor antigens. In recent years, researchers are more inclined to use computer and bioinformatics technology to find DNA nucleotide sequence. Then, they are also synthesized mRNA templates for research. Moreover, proteomics technology can also be used for antigen screening analysisthough their accuracy still requires much progress in the future.

6. Conclusion

This paper mainly discusses the new mainstream technologies of therapeutic cancer vaccines: cellular vaccines (autologous tumor cells, allogeneic tumor cells), peptide vaccines (long peptide cancer vaccines, personalized peptidyl cancer vaccines) and nucleic acid cancer vaccines (DNA vaccines, RNA vaccines). The following is a summary of the vaccines described in this article(Table 2).

Table 2. Summary of Three Therapeutic Vaccines

Classification		Main advantage	Main disadvantage
cell	autologous tumor cell	individuation	great difference in curative effect
	allogeneic tumor cells	effective	may have poor memory
peptide	long peptide	lasting	possibly poor immunogenicity
	personalized peptidyl	precision	high cost and complexity
nuclein	DNA	efficient and flexible	instability
	RNA	efficient and simple	instability

To sum up, we can make the best choice based on the actual needs of patients and the characteristics of different cancer vaccines. For example, if patients want a faster therapeutic effect, nucleic acid vaccines can be selected. But no option is 100% stable. So in order to ensure success in actual clinical treatment, we tend to use combinations. Combination is a relatively common approach in the field of cancer immunotherapy.

The principle of combination is based on the complexity of the immune system and the heterogeneity of the cancer. Because different vaccines target and different types of cancer cell antigens may activate the immune system through different mechanisms. Therefore, many vaccines are used in combination

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to improve the strength and the persistence of the immune response. What is more, it can solve the problem on resistance to monotherapy. Thus, cancer cells can be removed more effectively .The goal of prolonging the survival of patients can be achieved. Combination is divided into the following three types. The first is the combination of vaccines and vaccines, especially the combination of different types of vaccines. For example, combining the DC vaccine with allogeneic tumor cells can activate both humoral and cellular immunity, which can produce a more comprehensive immune response. Secondly, vaccines and immune checkpoint inhibitors can also be combined. For example, the combination of PD-1/PD-L1 inhibitors. This is one of the most common ways of combining. PD-1/PD-L1 inhibitors can remove the suppressed state of the immune system, so that T cells can better play an anti-tumor role. For example, the aforementioned mRNA cancer vaccine MRNA-4157 is combined with anti-PD-1 monoclonal antibody Keytruda to treat melanoma patients. Currently, clinical trials have shown that the combination therapy significantly reduces the probability of tumor metastasis and recurrence. Finally, there is the combination of vaccines and other immunotherapies. Because some vaccines take time to design and produce, and they also take time to be effective. Therefore, the vaccine can be used in combination with other immunotherapies such as CAR-T cell therapy and oncolytic viruses. These combination therapies can complement each other to increase the rate and effectiveness of treatment. Of course, the clinical application of combination faces great challenges. For example, how to determine the best combination design, how to determine the combined dose and administration time, how to reduce the cost of treatment. In the future, with more in-depth research on cancer immunotherapy and much progress of technology, therapeutic cancer vaccines will certainly play a more important role in cancer treatment.

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