The Development and Future Perspectives of Cancer Vaccines

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Abstract

The invention and application of vaccines are remarkable progress in the approach of defense against diseases. Due to vaccines, in addition to treatment after infection, the strategies for curing have expanded to prior prevention. Cancer vaccines are cancer immunotherapies that trigger artificial immune responses against TAAs and TSAs to utilize immune memory to attack and destroy malignant tumor cells. Although cancer vaccines, which utilize the immune system to maintain the inner balance of the human body, are revolutionary compared to conventional chemotherapy, the variety of TAAs and TSAs, systemic toxicity, and low immunogenicity of tumor antigens have hindered cancer vaccines' clinical use. This paper gives a brief review of cancer vaccines along with other immunotherapy methods. It will investigate the types, development, and mechanism of cancer vaccines and other immunotherapy. It will also compare cancer vaccines with other cancer immunotherapies and discuss the prospects of cancer immunotherapies. Cancer vaccine has a huge potential to control the development of cancer. This paper hopes to summarize and review the future trend of cancer therapeutics and promote the acquaintance with cancer vaccines.

Keywords: Cancer Vaccines; Tumor-Associated Antigens; Immunotherapies

Introduction

Cancer is a highly fatal disease caused by the accumulation of genomic mutations. These mutations lead to uncontrolled proliferating body cells, which can be defined as cancer cells. Cancer cells metastasize inside the body, destroying normal tissues and ultimately causing the death of the patient. However, due to their mutations, cancer cells also bear specific proteins called tumor-associated antigen (TAA) and tumor-specific antigen (TSA) on their surfaces. The former is expressed at a relatively low level in normal cells but at a high level in tumor cells. New peptide chains caused by mutations generate the latter and, therefore, does not exist in normal cells. The immune system utilizes TAA and TSA to recognize and eliminate cancer cells.

Nevertheless, cancer cells can disable the immune system to achieve the escape phase of immunoediting, and that's where cancer vaccines intervene. The basis of vaccines is antigen, i.e., inactivated or weakened viruses or bacteria, which enables the immune system to recognize the invading pathogen. After recognition, the immune system produces antibodies to fight the disease and remember it.[1] The cancer vaccine is based on a similar principle, utilizing TSA and TAA to trigger the immune response against cancer cells again.

Cancer vaccine is a type of cancer immunotherapy. Humans have been searching for a cure for cancer for centuries. The earliest record of cancer dates back to 1600 BC in ancient Egypt when papyrus records of eight cases of burning-treated breast tumors were found. Cancer remains highly fatal until now. According to WHO's recent statistics, cancer had caused 9.96 million deaths (59.23 million total) in 2020.[2] But cancer immunotherapy has made a difference. In 2013, Bristol-Myers Squibb reported that after their anti-CTLA-4 therapy with Ipilimumab, 22% of 1800 melanoma patients lived three years later, making cancer immunotherapy Breakthrough of the Year of Journal Scientist in 2013.[3] The newer treatment strategies like blocking inhibitory checkpoints or cellular therapy have marginalized cancer vaccines in this field. However, mRNA vaccines against COVID-19 have restored focus to cancer vaccines. Nonetheless, this cure method against cancer and the concept of immunotherapy remain unfamiliar to the general public. Therefore, this paper briefly reviews cancer vaccines, which aims to provide the public with a basic understanding of cancer vaccines and the dynamic relationship between cancer and the immune system.

Like normal vaccines, there are two categories of cancer vaccines: preventive and therapeutic. But cancer is the result of joint actions, including radiation, chemicals, and unhealthy habits besides viruses, so in this paper, the cancer vaccine only refers to the therapeutic one.

1. Cancer immunotherapies

Cancer immunotherapies can be classified into five types: oncolytic virus therapy, cytokine, adoptive cell transfer, checkpoint inhibitor, and cancer vaccine.

Cancer is normally treated through chemotherapy and targeting drugs. Chemotherapy is one of the three major methods to treat cancer with radiotherapy and surgical

resection. Chemotherapy utilizes cytotoxic drugs to eliminate cancer cells. However, cytotoxic drugs don't possess the ability to lock on a specific type of cell accurately. Cancer cells are simply more sensitive to the drug's toxicity. Therefore, chemotherapy destroys normal somatic cells alone, namely having a relatively low therapeutic index, and induces obvious side effects, including digestive system reaction (vomiting, diarrhea, and astriction), myelosuppression, alopecia, and damage of level and renal function. Targeting drugs is based on the progress in research on gene mutations. It focuses on the driver mutation of cancer cells and designs a specific chemical compound to inhibit target activity. The driver mutation varies according to the type of cancer. Consequently, targeting drugs has extremely high specificity. However, a significant characteristic of cancer is its susceptibility to mutation, which means targeted drugs may fail during the treatment process.

The immune system uses the biochemical makeup, antigenic structure, and biological behavior of cancer cells for differentiation. Then, the immune system will destroy them. But cancer cells have evolved multiple mechanisms, including core cancer intrinsic immune evasion genes, transporting mitochondrion from immune cells [4], and expressing immune checkpoint molecules like normal cells to evade the immune system. But chemotherapy and targeting drugs fail to bring the system of cancer cells and immune cells back to the stage of immune surveillance, where the immune system can recognize and promptly clear mutated cells. Compared with traditional therapies, cancer radiotherapy, chemotherapy, and targeting drugs, the most prominent feature of cancer immunotherapy is that it cancan reactivate the patient's immune system to suppress cancer. Immunotherapy is aimed at terminating the immune escape of cancer cells. However, it should be noted that immunotherapy must achieve a balance between boosting the immune system to attack cancer cells and not producing autoimmune inflammatory responses.

1.1 Oncolytic virus therapies

Oncolytic virus therapy uses genetically modified or naturally occurring viruses that selectively kill cancer cells and won't destroy healthy or normal tissue. [5] It is the most ancient immunotherapy strategy. It uses a caner-selectively killing virus. The discovery by the father of immunotherapy, William Coley, in 1891 that the mixture of live and inactivated streptococcus pyogenes and Serratia marcescens could cause regression of sarcoma can be perceived as its prototype. [6] Then, the rabies virus was used to target cervical cancer in 1912.[7] However, due to the unknown underlying mechanism and risk of infection, this therapy was shelved.

Genetic engineering boosted it. In 1991, herpes simplex virus-1 was proved to target brain tumor cells in experiments. The FDA approved Talimogene laherparepvec (T-VEC) in 2015, a genetically modified HSV-1 to treat advanced melanoma.

1.2 Cytokines

Cytokine functions as the messenger between immune and nonimmune cells, enabling the immune system to react efficiently against target antigens. Identifying interleukin-2 (IL-2) in 1976 demonstrated its potential in cancer treatment. IL-2 can expand T-cells in vitro and in vivo, thus exerting immune-stimulatory properties.[8]

Cytokines was originally approved for clinical use in 1998 to treat kidney cancer and melanoma. However, this method is hindered by significant treatment toxicity. [9] Research is currently focused on reducing toxicity and drug combinations.

1.3 Adoptive cell transfer

Adoptive cell transfer reinfuses genetically engineered autologous immune cells into patients to destroy cancer cells. These cells are particularly T-cells. [8] Chimeric antigen receptor T cell (CAR-T cell) and T cell receptor engineered T cell (TCR-T cell)are engineered T-cells.

CAR-T cell is T cells binding with the receptor of B cells, which allows T-cells to differentiate tertiary protein directly, thus simplifying the procedure of T-cells to recognize cancer cells. TCR-T cells are to present the MHC of cancer cells to T-cells artificially to enable T-cells to lock on cancer cells.

TCR-T cells and CART-T cell therapies have generated encouraging outcomes, but their treatment progress, which lasts around five weeks, is painful, and cultivating tens of millions, even hundreds of millions of cells, is risky.

1.4 Checkpoint inhibitors

Checkpoint inhibitors are the application of theoretical breakthroughs in immunology, and Checkpoint inhibitors remove these brakes to enable T-cells to kill cancer cells again. Cancer cells utilize the brakes of the immune system to evade immune surveillance. Two main immune checkpoints exist: cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) and programmed cell death receptor-1 (PD-1).

Pierre Golstein first proved the existence of CTLA-4 in 1987. Dr James Allison's discovery that CTLA-4 prevents T-cells from a full immune response followed this. He hypothesized that T cells would retrieve the ability to attack and kill the cancer by blocking CTLA-4 molecules. [6] This discovery laid the foundation for Ipilimumab, which is against metastatic melanoma and was approved

by the FDA in 2011, becoming the earliest checkpoint inhibitor drug in the market.

Dr Drew Pardoll discovered PD-1, which was originally considered to be involved in programmed cell death.[10] However, following discoveries revealed that it binds with its ligand PD-L1 to suppress lymphocyte proliferation and cytokine secretion. The ligand was discovered by Yasumasa Ishida and Tasuku Honjo in 1992. At present, PD-L1 has been approved for the treatment of lung cancer. [11]

The range of checkpoint inhibitors' application is limited. It only shows effectiveness on hot tumors, but combination therapy can complement this limitation.

1.5 Cancer vaccines

Cancer vaccines utilize tumor-associated antigens (TAA) or tumor-specific antigens (TSA) to stimulate patients' immune system against cancer cells. [8] TAA can also be expressed on surfaces of normal tissues and cells, but the expression level on cancer cells far exceeds the level on normal cells. At the same time, TSA is a novel antigen that is only expressed on tumor cells and does not exist in normal tissues or cells. Both TAA and TAS are tumor antigens. They are molecules on the surfaces of cancer cells and can trigger an immune response that leads to the destruction and elimination of agents. They are classified according to specificity. They can trigger humoral immunity and cellular immunity to recognize and then extinguish cancer cells, and TSA triggers mainly T cell immune response. B cells undertake humoral immunity, presenting antigens to CD4 T cells and inducing the immune response of CD4 T cells to tumors. Cellular immunity involves T cells, N.K. cells, macrophages, and dendritic cells. The four kinds of immune cells function differently. Dendritic cells participate in the presentation of tumor antigens. N.K. cells can induce the apoptosis of target cells. Macrophages cause the lysis of cancer cells, and antigen-sensitized T cells specifically destroy cancer cells. Other immunotherapies have revealed the interaction between cancer cells and the immune system; thus, the development of cancer vaccines is boosted. Key factors of the efficacy of cancer vaccines are the immune landscape of the tumor and the vaccine formulations. CD8+ T cells play a vital role. They display intense cytotoxic mediators to tumor antigens. The study has shown a correlation among CD8+ T cell response, clinical response, and overall survival in vaccinated patients. So, this type of T cells can be a biomarker to evaluate cancer vaccines.[12]

This is a challenging therapeutic method. It appeared to be the earliest, but the outcome of this method is limited. Coley's toxin could be recognized as a kind of vaccine as it triggered specific responses against sarcoma antigens. [13] Following this, bacillus Calmette-Guerin (BCG) vaccines were used against cancer cells. But BCG had caused fatalities and resulted in cancer vaccines being shelved. In 1976, research led by Dr. Alvaro Morales provided evidence of the effectiveness and safety of BCG in treating superficial bladder cancer, which brought attention to it. [14] And there exist only two types of cancer vaccines that are approved for therapy at present. They are BCG for bladder cancer and Provenge for prostatic cancer.[15]

Four types of cancer vaccines exist, which are classified according to the form of delivered antigens. The four types include cell-based, peptide-based, viral-based, and nucleic-acid-based vaccines.[16]

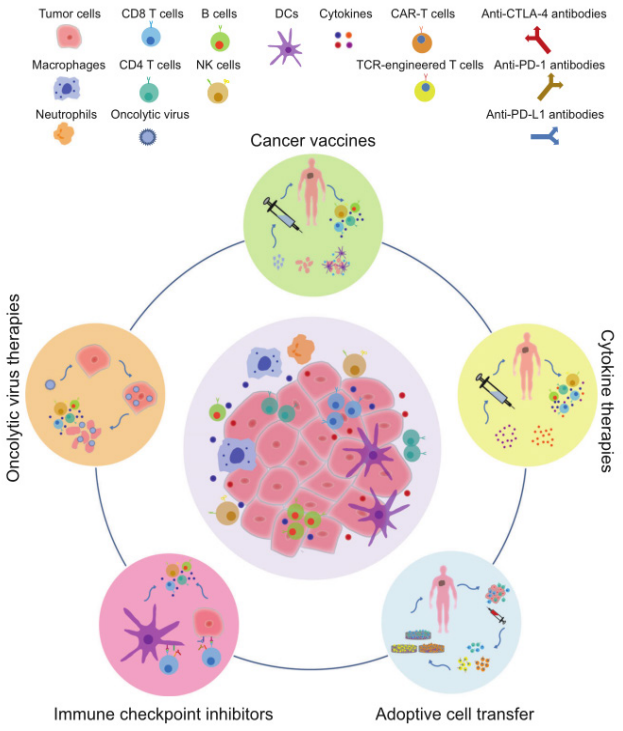

Figure 1 The major categories of immunotherapy.

Different forms of cancer immunotherapy, including oncolytic virus therapies, cancer vaccines, cytokine therapies, adoptive cell transfer, and immune checkpoint inhibitors, have evolved and shown promise in clinical practice. The basic principles of each strategy and the corresponding cellular and molecular underpinnings involved in each step are depicted. D.C.s dendritic cells, N.K. natural killer, TCR T-cell receptor, CAT-T chimeric antigen receptor T-cell. Cited from Zhang Y, Zhang Z. The history and advances in cancer immunotherapy: understanding the characteristics of tumor-infiltrating immune cells and their therapeutic implications. Cell Mol

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2. Cancer vaccines

2.1Cell based vaccines

Cell-based vaccines contain tumor cell vaccines and dendritic cell vaccines (D.C. vaccines). Tumor cell vaccines use whole tumor-associated antigens, while dendritic vaccines use dendritic cells to load a variety of tumor antigens.

Tumor cell vaccines are vaccines produced by genetically modifying cancer cells. The difficulty of obtaining a sufficient number of cells has limited this type of vaccine. [17] However, cultivating a sufficient number of dendritic cells is possible; thus, this dilemma is able to be avoided. [18]

Up to now, this approach has been attempted to treat many kinds of tumors, including lung cancer, colorectal cancer, melanoma, renal cell carcinoma, and prostate cancer. [17] The attempt targeting prostate cancer is the most successful. In 2010, Provenge was approved by the FDA as a prostate cancer vaccine.[17]

Cancer is classified by cell or tissue type, including carcinoma, sarcoma, myeloma, leukemia, lymphoma, melanoma, and the rest. There are hundreds of different types of cancer, so why do those types above have the possibility to be cured by vaccines? The reason is that they're all hot tumors. Hot tumors are also referred to as infiltrative types, which means they are infiltrated by a great number of T cells. The infiltration process involves T cells migrating to the tumor, identifying the tumor, and killing the tumor cells. Therefore, hot tumors have a relatively higher efficacy of immunotherapy.

2.2Peptide based vaccines

Peptide-based vaccines use synthetic peptides, from which specific antigenic epitopes are derived, to develop cancer vaccines to trigger immunity. [16] Amino acid molecules connected by peptide bonds are peptide chains. Multiple peptide chains fold to form a protein molecule. Protein is the chemical composition of the antigen on surfaces of cancer cells. Hence, it is the preferable option to choose those not expressed on the surface of normal cells for peptide-based vaccines.

This type of vaccine is easy to manufacture and safer. However, its therapeutic efficiency is not satisfactory. The present achievements of peptide vaccines are only preventive vaccines, e.g., vaccines against HPV or HBV. HPV vaccine is also known as human papillomavirus vaccine. It's against papillomavirus, the infection that causes cervical carcinoma. This kind of vaccine introduces the L1 gene of the virus into yeasts or insect host cells. The L1 gene fragment will manipulate host cells to synthesize the capsid protein of papillomavirus (VLP). Then, the purified VLP will be injected into the human body to induce an immune response against papillomavirus. Meanwhile, since the active ingredient is just an empty shell, the infection is impossible. The specific categories of this vaccine, as well as the types of viruses and diseases they can prevent, are shown in the table below.

Table 1 Specific categories

Variety	Age range	Virus Type	Disease
Bivalent	Female aged 9-45	HPV 16/18	About 70% of cervical carcinoma Adenocarcinoma in situ and CIN caused by corresponding types
Tetravalent	Female aged 20-45	HPV 6/11/16/18	About 70% of cervical carcinoma Adenocarcinoma in situ and CIN caused by corresponding types Genital condyloma acuminatum
Nine valent	Female aged 16-26	HPV 6/11/16/18/31/33/45/52/58	About 90% of cervical carcinoma Adenocarcinoma in situ and CIN caused by corresponding types Genital condyloma acuminatum

2.3 Viral based vaccines

The prototype of viral-based vaccines can be traced back to Coley's toxin. An oncolytic virus is a novel approach to viral-based vaccines. Viral-based vaccines utilize oncolytic viruses to trigger antiviral immune responses. The immune system responds efficiently to viruses,

which is the advantage of viral-based vaccines. [19] The disadvantage of this type of vaccine is that an antiviral immune response can cause repeated immunizations to be difficult to achieve.[16]

Viral-based vaccines might complement the failure of other immunotherapy approaches. Tumors can be classified into hot tumors and cold tumors, which are two types. The pre-existing tumor infiltration with tumor-specific immune cells and a proinflammatory milieu are the characteristics of hot tumors.[20] This results in normal immunotherapies like checkpoint inhibitors being more effective. Cold tumors have a low mutation load and fewer T cells inside, leading to an immune response that is difficult to trigger and failure of immunotherapies. The oncolytic virus can avoid the problem of insufficient immune cells inside cold tumors by targeting the tumor cells' defect of the antiviral system.[21]

2.4Nucleic acid-based vaccine

Nucleic acid-based vaccines contain DNA-based and RNA-based vaccines. The most prominent characteristic of nucleic-based vaccines is that, unlike traditional vaccines, this type of vaccine contains no pathogen or parts of a pathogen. Nucleic acid-based vaccines vaccinate the process of specific protein synthesis in patients directly. A key challenge in this type of vaccine is to protect the nucleic acid from being degraded before reaching the target site.

DNA vaccines move into the cell nucleus to start transcription. In the nucleus, the DNA fragments mRNA to be translated to specific T.A.s by the host. [22] DNA cancer vaccine has passed early clinical trials and is used to treat a variety of prostate cancer and breast cancer. [16] But mRNA can skip the step of entering a nucleus as mRNA can directly be translated into the cytoplasm. This feature allows mRNA vaccines to perform better in immunogenicity. Furthermore, the COVID-19 pandemic has facilitated mRNA vaccine development, so the perspective about cancer vaccines can be focused on mRNA.

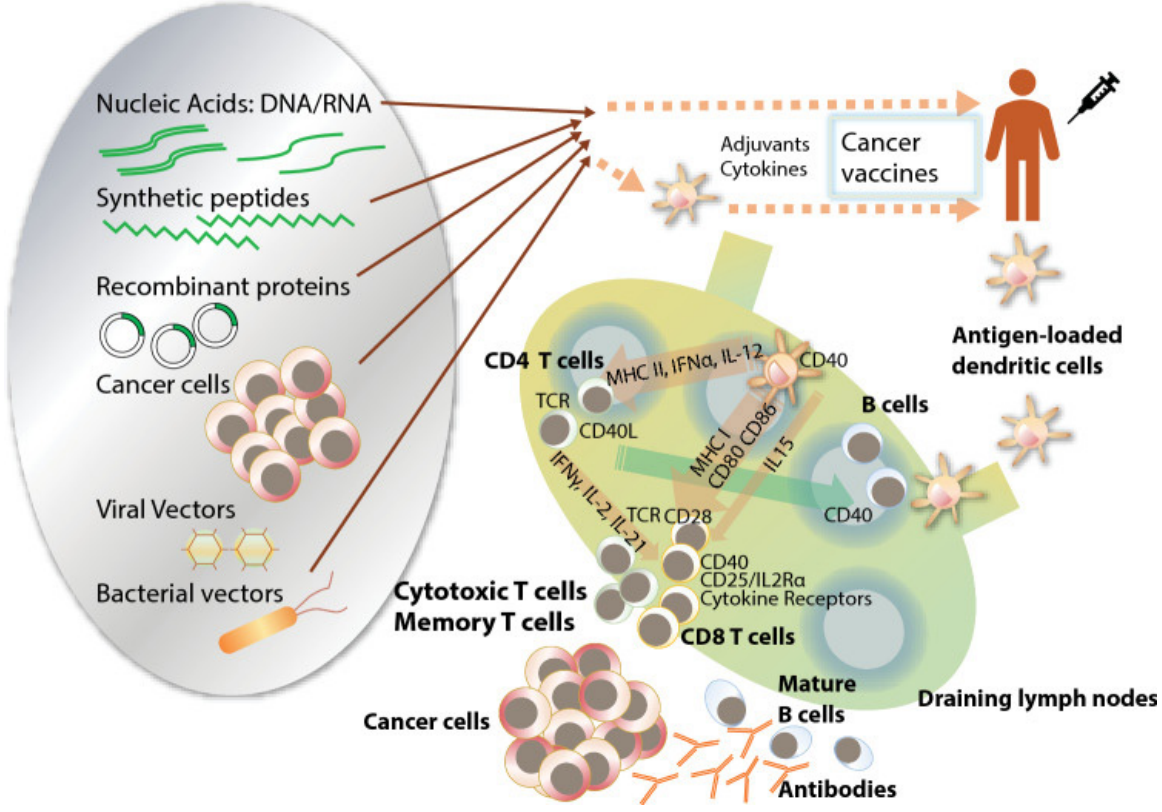

Fig. 2 Diverse therapeutic cancer vaccine platforms have a common mechanism of action. CD cluster of differentiation, IFN interferon, I.L. interleukin, IL2Rα IL-2 receptor alpha, MHC major histocompatibility complex, TCR T cell receptor. Cited from: Maeng H et al. F1000Res. 2019 https://doi.org/10.12688/f1000research.18693.1. Licensed under CC BY 4.0.]

3. Latest development of cancer vaccine

To date, replicating modified mRNA, unmodified mRNA,

and virus-derived mRNA are the three main types of mRNA vaccines in cancer immunotherapy. [23] According to ClinicalTrails.gov, the recently completed trials of mRNA vaccines are shown in the table below.

Table 2 Completed mRNA vaccine trials

Row	Study title	Conditions
1	Phase 1/2 Study of Combination Immunotherapy and Messenger Ribonucleic Acid (mRNA) Vaccine in Subjects With NSCLC	Metastatic Non-small Cell Lung Cancer NSCLC
2	Safety and Efficacy Trial of an RNActive®-Derived Prostate Cancer Vaccine in Hormone Refractory Disease	Hormonal Refractory Prostate Cancer
3	A Trial of the Safety and Immunogenicity of the COVID-19 Vaccine (mRNA-1273) in Participants With Hematologic Malignancies and Various Regimens of Immunosuppression, and in Participants With Solid Tumors on PD1/PDL1 Inhibitor Therapy, Including Booster shot	Solid Tumor Malignancy Hematologic Malignancy Leukemia Lymphoma Multiple Myeloma
4	Trial of Vaccine Therapy With Transfected Dendritic Cells in Patients With Advanced Malignant Melanoma	Malignant Melanoma
5	Trial of Vaccine Therapy With Transfected Dendritic Cells in Patients With Androgen-Resistant Metastatic Prostate Cancer	Prostate Cancer
6	Peptide-pulsed vs. RNA-transfected Dendritic Cell Vaccines in Melanoma Patients	Melanoma Stage III or IV

Compared with other immunotherapies, mRNA vaccines have prominent strong points. It provides safe vaccination, improving antigen expression and avoiding gene integration.[24] It can able to manufacture like peptide vaccines, and it doesn't need to go through the long process of CAR-T therapy, which consists of drawing blood, isolating T cells,tivating T cells, and then reinfusing T cells into the patients. In addition, injecting multiple types of T.A.s simultaneously helps it respond to the mutation problem of cancer better. But mRNA vaccines still face the same dilemma, which is the unknown field in cancer immunoediting, as other methods of immunotherapies.

4. Conclusion

Cancer vaccines can be basically classified into four types, which include cellular vaccines, peptide/protein vaccines, viral vector vaccines, and mRNA/DNA vaccines. Their essential mechanism is artificially stimulating the immune system of cancer patients to trigger an immune response against tumor-associated antigens (TAA) and tumor-specific antigens (TSA).

Cancer vaccines are revolutionary as they reactivate patients' own immune systems. Immunotherapy is based on the mechanism of a tumor's immune escape. Compared to other treatment methods of cancer, cancer vaccines, along with other immunotherapies, target cancer cells more accurately and can cause relatively minor side effects to patients. This conforms more to the future trend of precision medicine. However, different types of cancer vaccines have their own disadvantages and have their own boundness to break. Cell-based vaccines need to cultivate cells from the patient's own body, which makes it difficult for them to decrease the cost of treatment. They also face the difficulty of different characteristics of cold and hot tumors. Peptide-based vaccines may perform weaker in triggering a strong enough immune response, although they are easy to manufacture. Virus-based vaccines are effective against cold tumors, but repeated immunizations may be difficult to achieve.

Cancer vaccines cease the immune escape of cancer cells to prevent cancer cells from unlimited proliferation, but many of tumor's escape methods remain unknown. The common problems like failure or toxicity that cancer vaccines are facing are raised from the misty area of immunology. Therefore, the future perspectives of cancer vaccines and other immunotherapies depend on the development of fundamental subjects. Besides, the significant difference in curative effect between hot tumors and cold tumors is another key point to facilitate a new breakthrough in cancer vaccines. The future development of cancer vaccines may also lie in the conversion from cold tumors to hot tumors.

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