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A review on cancer vaccines: Current developments and future prospects

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Abstract

Tumour immunotherapy has made tremendous progress in the past decades, with numerous studies entering the clinical evaluation. The cancer vaccine is considered a promising therapeutic strategy in the immunotherapy of solid tumours. Cancer vaccines stimulate antitumor immunity using tumour antigens, which can be delivered as whole cells, peptides, nucleic acids, etc. An ideal cancer vaccine would be able to overcome tumour immunosuppression and induce both humoral and cellular immunity. The use of cancer vaccines is considered a promising therapeutic strategy in clinical oncology, which is achieved by stimulating anti-tumour immunity with tumour antigens delivered in the form of cells, peptides, viruses and nucleic acids. The ideal cancer vaccine has many advantages, including low toxicity, specificity, and induction of persistent immune memory to overcome tumour heterogeneity and reverse the immunosuppressive microenvironment. Cancer treatment is done by surgery,chemotherapy,radiation therapy. These treatments may cure early-stage cancer, but are often ineffective in treating advanced or recurrent cancer. Basic and clinical studies of the tumour microenvironment, which consists of cancer cells, stromal cells, and immune cells, have demonstrated the important role of antitumor immunity in cancer development and progression. Cancer immunotherapy has been proposed as a fourth cancer treatment option. In particular, the clinical application of immune checkpoint inhibitors, such as anti-CTLA-4 and anti-PD-1/PD-L1 antibodies, to various types of cancer represents a major advance in cancer treatment. Indeed, several issues remain to be solved to improve their clinical efficacy; these include low cancer cell antigenicity and poor infiltration and/or accumulation of immune cells in the cancer microenvironment.

Keywords: Cancer vaccine; Tumour antigen; Tumour resistance; Immunotherapy; Clinical application

1. Introduction

Cancer vaccines are a type of immunotherapy that aims to stimulate the body's immune system to recognize and attack cancer cells. Cancer is one of the leading cause of death. This is largely due to has. that people tend to live longer, with fewer people dying from other causes such as infectious diseases. In 2000, over 6 million people died from and there were an estimated 10 million new cases. Between 2000 and cancer 2020 the total number of cases of cancer is predicted to increase by 73% in the developing world and by 29% in the developed world, largely as a result of demographic shift in geriatric population'. A report on the incidence of common cancers in India in 2004 showed it as around 154 thousands and 267 thousands in males and females respectively During the past two decades, data on diet and cancer have greatly increased and this reinforces the belief that a substantial proportion of cancer is potentially preventable by nutritional means. Quantitative estimates of the preventable proportion in Western countries remain approximately 30% to 40%. Presently there is abundant information on specific aspects of nutrition. The relationships between specific dietary components and cancers are less well established than that of diet and cardiovascular disease. This is due to the fact that the role of diet in the causation of cancer has always been difficult to study and quantify partly because the diet encompasses wide variety of foods, dietary traditions. habits and is a complex mixture of nutrients and non nutrients.

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1.1. Background

The advent of vaccines has introduced new opportunities to prevent and treat infectious diseases. The earliest vaccine can be traced back to 1796 when Edward Jenner found that the cowpox vaccine protects against smallpox infection [1]. As the vaccine developed, it was later introduced to treat more diseases, such as cancers. The initial cancer vaccine based on tumour cells and tumour lysates was developed in 1980. Scientists used autologous tumour cells to treat colorectal cancer [2]. In the early 1990s, the first human tumour antigen melanoma- associated antigen 1 was identified [3], which opened a chapter on using tumour antigens in cancer vaccines. In 2010, a dendritic cell-based vaccine(Sipuleucel-T) was successfully used to treat prostate cancer, proving the viability of cancer vaccines and creating great excitement in the cancer vaccines field [4]. The outbreak of COVID-19 has urged the development of vaccine technology and brought cancer vaccines back into the public focus. Cancer vaccines mainly use tumour-associated antigens (TAAs) and tumour-specific antigens (TSAs) to activate the patient's immune system. Theoretically, the vaccine could provoke both specific cellular immunity and humoral immune response to prevent tumour growth and ultimately eradicate tumour cells [5]. Currently, most cancer vaccines are still in the stage of preclinical and clinical research [6]. More specific antigens and vaccine development plat forms need to be developed.

2. Mechanism of cancer vaccine tumour antigens

Antigen selection is a key process in cancer vaccine development. Tumour antigens recognized by T lymphocytes play a central role in the efficacy of cancer vaccines [7]An ideal antigen for a cancer vaccine should be highly immunogenic, clearly expressed in all cancer cells (but not in normal cells), and essential for cancer cell survival [8] Humans are prominent examples of overexpressed tumor antigens, such as epidermal growth factor receptor 2 (HER2) and human telomere reverse transcriptase [9]. Tissue differentiation antigens are expressed by tumor cells and normal cells of the same origin as the tumor cells.

For example, prostate-specific antigen (PSA) is expressed in the prostate and prostate cancer. Tyrosinase is expressed by normal melanocytes and melanoma cells [10]. AAT is adaptable and can be used for a variety of patients. Early cancer vaccines mainly focused on TAAs. However, due to central immunity, thymic tolerance activation T cell recognition TAAs or other self-antigens may be eliminated during treatment. Development affects the efficacy of vaccines [11]. Therefore, cancer vaccines using TAAs are convincing enough to "break tolerance". Although TAAs have been of interest for many years, clinical trials of TAA-based cancer vaccines have had limited success [12].

Furthermore, TAAs are also expressed in non-malignant tissues, thus increasing the risk of vaccine-induced autoimmune toxicity.TSAs are a class of proteins that are specifically expressed in tumor cells. ASDs are also called neoantigens. Individually specific non-self proteins, produced by mutations in tumor cells, are called neo-antigens [13].

Neoantigens are expressed only by tumor cells that trigger true tumor-specific T cell responses with limited "off-target" damage [14].Compared to TAAs, neoantigens have stronger immunogenicity and higher affinity for major histocompatibility complex (MHC). Moreover, it is not subject to central authority. Immune tolerance [15]. The widespread use of next- generation sequencing technology allows to identify individualized neoantigens in a rapid and cost-effective manner. We also developed algorithms to predict MHC class I binding epitopes, which has greatly facilitated the discovery of new potential immunogenic epitopes [16]. Cancer vaccines targeting neo antigens have become the primary goal of vaccines against tumors... Recently, they have been evaluated in several clinical trials. Neoantigen vaccines have shown promising results Improved patient survival [17]. Melanoma vaccines Neoantigen-like mRNAs are a classic example, inducing T cell infiltration and neoantigen-specific killing of autologous tumor cells . The metastatic event rate was significantly reduced after vaccination, and there was a sustained progression-free survival [18]. In addition,vaccination with neoantigen-loaded DCs could induce TLiu et al. Journal of Hematology and Oncology.

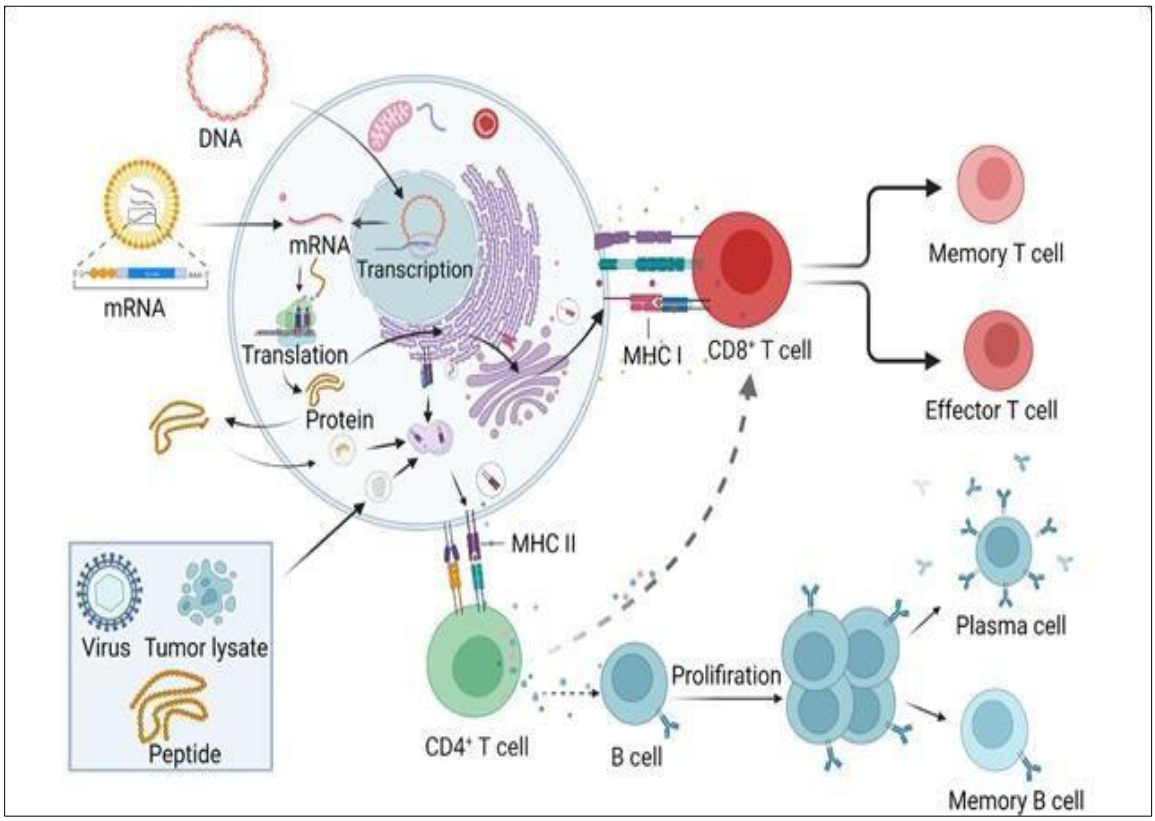

Figure 1 Mechanism of cancer vaccines. Compared to peptide-based vaccines, nucleic acid-based vaccines need more processing steps after entering the body before being presented to T cells by DCs. However, DNA and RNA vaccines are better suited to deliver MHC I presentation antigens than peptide vaccines. Tumor antigens are processed by DCs and transported to the cell surface of MHC I and MHC II molecules. Interaction between MHC–peptide complex–T cell receptor (TCR) and cognate receptor- ligand pairs activate T cells. Activated CD4+ T cells induce B cells to differentiate into plasma cells and memory B cells. Activated T cells differentiated into CD8+ memory T cells and CD8+ effector T cells. Eventually, effector T cells, B cells, antibodies, and some cytokines kill tumor cells directly or indirectly

3. Cancer vaccine platforms

Cancer vaccines can be classified into four categories:

cell-based vaccines, peptide-based vaccines, virus-based vaccines, and nucleic acid-based vaccines (Figure 1) Cell-based vaccines are initially the form of cancer vaccines.Cell- based cancer vaccines are often prepared from whole cells or cell fragments, containing almost tumor antigens, inducing a broader antigenic immune response.DC vaccine is an important field of cell-based vaccines. Personalized cancer vaccines based on DC-based neoantigens have shown promising antitumor effects in clinical trials. However, the development of DC vaccines has been limited by the cumbersome process and high costs. Viruses are naturally immunogenic and their genetic material has been engineered to contain sequences that code for tumor antigens. Several recombinant viruses, such as adenoviruscan infect immune cells as vectors. Engineering virus Vaccines can represent tumor antigens in large quantities The immune system produceantitumoral immunity.

In addition, oncolytic viruses can also be used as vectors. In addition to delivering tumour antigens, the virus itself can also lyse tumours and release tumour antigens, further enhancing the efficacy of the vaccine and creating long-term immune memory. However, the process of producing a viral vector-based vaccine is complex. Peptide-based subunit vaccines, which include chemical and biosynthetic preparations of predicted known specific tumour antigens, induce a robust immune response against a specific site of the tumour antigen. Based on peptides The subunit of the vaccine in combination with adjuvants can effectively provoke a humoral immune response suitable for Pre Ventilation and treatment of viral infectious diseases. HBV and HPV vaccines for liver and cervix cancer were primary or peptide peptides -based vaccines. In particular, subunit vaccines based on virus-like particles (VLPs), which can

activate cellular immune responses, have the shown excellent antitumor activity in recent years. Nucleic acid vaccines are a promising vaccine platform.

4. Cell based cancer vaccines

Cell-based vaccine can be divided into tumour cell vaccine and immune cell vaccine. Whole tumour cell vaccine is a relatively simple and direct approach to tumour immunotherapy. Tumour cell vaccines contain the following components: Whole tumour-associated antigens including epitopesCD4+ and CTL helper cells. Cellular immune vaccines Based on the role of cells in the immune system. DCs are the most powerful specialized agro-industrial complexes in the body. In most cases, DCs are required to present cancer antigens during vaccination. Therefore, an effective way for antitumor immunity is to import tumour-associated antigens into DCs to induce them to play the role of antigen presentation and activate T cells. Most DC vaccines are derived from monocyte-derived dendritic cells [19]. In immunotherapy studies, tumour cell lysates were loaded into monocyte-derived dendritic cells, and Mo DC-based vaccination was shown to be well tolerated and effective. The focus of DC-based vaccines was not only DC cells themselves; the exosomes released by dendritic cells were paid attention. DC exosomes are inert membrane vesicles with bio stability, which can express MHCI, MHC II, and co stimulatory molecules. Dendritic cells have already shown efficacy in the treatment of cancer in clinical trials. However, dendritic cells have yet to demonstrate clear clinical benefit [20].

5. Current progress in cell based cancer vaccines

In addition, photo sensor-induced dead and ferroptosis tumour cells RAS-selective lethality 3- induced immunogenicity may also be strongly immunogenic [21]. Modification of tumour cells may also improve the efficacy of whole tumor cell vaccines.In most cases, the purpose of the modification is to improve antigen presentation. This means that molecules related to the immune response may be involved the modification. For example, IL-21 and IL-7 are two important factors that can synergistically enhance T cell responses.

There is a vaccine with tumor cells with genetic modifications The IL-21 and IL-7 cation showed more efficiency. Double IL-15 transfector, NK modulator and memoryCT26 T cells and cut-off IL-15Rα receiver The cells also guided a reliable antitumor reaction. Furthermore, several adjuvant modification approaches have been used to modify vaccines, for example, dying tumor cells modified with CpG-loaded nanoparticles were found to enhance antigen presentation (22).Finally, the combination of whole tumor cell vaccines with immune checkpoint inhibitor (CPIs) is becoming more common. It is designed to block pathways that suppress activity auto reactive T cells. Programmed blocking of cell death-ligand 1 (PD-L1) and cytotoxic T lymphocyte protein 4 (CTLA-4) has already be demonstrated improve cell performance in therapeutic vaccinations [22]. Optimization of immune cell- based vaccines, especially DC vaccines, may involve more detailed information.

5.1. Virus-based cancer vaccines

One of the main advantages of virus -based vaccines is that the vaccine can make an innate and adaptive immune work together to reach effective and long Immune response. The virus-based vaccine can be divided into three forms: inactivated, displayed living, or subunits against the virus that can cause a tumour. Oncolytic virus vaccine and VEC virus vaccine. The incidence of cancer is reported to be about 12%.

It is believed to be caused by viral infections. Epstein-Barr virus, hepatitis B virus, hepatitis C virus, and HPV are the most common viruses associated with cancer [23]. Inactivated whole virus vaccines have shown promising efficacy in the treatment of COVID-19 and Ebola [23]. Logically, they would show similar efficacy in the treatment of virus-associated cancers [23]. However, he noted that they are probably not used much in cancer probably because of production difficulties and safety concerns. Instead, with developments in bioengineering technology, virus-like particle approaches are increasingly being used for therapy. Oncolytic viruses are a novel immunotherapy that kills tumour cells and stimulates antitumor responses. Upon infection with oncolytic viruses, tumour cells produce ROS and cytokines that stimulate immune cells. Subsequently, oncolysis will occur and substances such as TAA will be released [24]. Various clinical trials have already proven the antitumor efficacy of oncolytic viruses. Oncolytic viruses include herpes simplex virus, adenovirus, measles virus, vaccine virus, retrovirus, and vesicular stomatitis virus. Among them, T-VEC, a first-generation recombinant product of herpes simplex virus, was the most striking. Besides herpes simplex virus, adenovirus is another widely used oncolytic virus, which is also often used as a delivery vectors for certain genes [24]. Adenovirus is easy to handle, its gene structure is clear, and it is easy to reach the gene Transfer and

tumour expression of the antigen. Second, Adenovirus has a very broad spectrum of host cell tropism and it can be quickly prepared in large quantities. In addition, mucosal infection is an inherent feature of adenoviruses. Therefore, the adenovirus vector is a promising vaccine platform. Adenovirus-based promise in preclinical and clinical trials [25]. Except for adenoviruses, other vectors such as vaccines, lentiviruses, and adenovirus- associated viruses are also used in tumour vaccine platforms. Lenti viruses and adenovirus- associated viruses have the unique ability to achieve stable and long-term expression of transgenes in non-dividing cells. As adenoviruses.

5.2. Peptide-based cancer vaccine

The current focus of cancer vaccines is converting whole, inactivated, or attenuated pathogens into subunit vaccines. Peptide vaccines are polypeptides made from known or predicted tumour antigen epitopes. Due to the limitation of MHC polymorphism and the small size of antigen epitopes themselves, the immunogenicity of peptide-based vaccines is weak. It is often difficult to cause a robust immune response, which also leads to immune tolerance. Adjuvants are combined with vaccines based on peptides to strengthen the immune response in general. No All areas of protein antigens are also immunogenic For C cells and t cells. Compared to inactivated tumour cell vaccines, peptide-based vaccines induce a more targeted immune response against key neutralizing epitopes. This advantage in immunity is called immunodominance [26]. Peptide-based cancer vaccines usually require both CD8+ and CD4+ T cell epitopes. CD8+ T cell epitopes activate CTL antitumor immunity through the antigen cross-presentation pathway, while CD4+ T cells activate helper T cells to maintain CTL function. The length of the peptide chain is mostly determined Peptide sources performance. There is a short peptide Usually, the smallest epitope CD8+ T cells and short Half in vivo. Peptide TIS does not require special APC treatment and is directly responsible. MHC I APC molecular or other nuclear cells. Absurd Cost Maral molecules required for the optimal CD8 + T CTL provocation is restricted by cell activation. Thus, short peptides often activate CTLs transiently and also induce tolerance to CTLs [26]. Moreover, by being short, peptides also tend to be HLA type restricted. Compared with short peptides, long peptides can provide broader HLA coverage, including multiple epitopes, while also supporting motif recognition and binding for enhanced immunogenicity. Long peptides need to be processed by APCs rather than being directly loaded onto MHC molecules [26]. After internalization, part of the long peptides decomposed by an endosomal way loaded into MHCII molecules, and then CD4+ T Helper is recognized other parts are in cytoplasmic or vacuole cells Way and cross molecules MHC-I Activate CD8+ T -cells [13]. Thus, long peptide vaccines have great potential to induce durable and effective antitumor responses. Short peptides are usually produced by chemical synthesis, while long peptides are often produced by protein expression systems. Immunogenicity varies among recombinant proteins subunit vaccines based on different expression platforms. Several expression platforms have been used to produce cancer vaccines, including Escherichia coli (E. coli), plants, yeast, insect cells, and mammalian cells. These proteins expressed by mammal cells The closest to the natural tumour antigen. Baculovirus insect cell are low -cost potential systems and are partially After modification of target protein [12].

5.3. Nucleic acid based cancer vaccines

The nucleic acid vaccine is coded the owner's tumour antigen and provides genetic information that produces antigen -based proteins with normal physiological activity.

Expressive tumour antigen can cause immunoscopic. Insurance is applied from cancer cells.Due to the ubiquity of enzymes, Differences in the structure of RNA, DNA and mRNA. DNA is more stable than mRNA and persists in the body for a longer period of time. Therefore, early nucleic acid vaccines were mainly focused on DNA vaccines. DNA molecules must enter the cell nucleus to start Transcription, MRNA enters the cytoplasm translate and express the antigen directly. Previously, MRNM The production of antigens is instantaneous and efficient. DNA vaccines require an additional step to enter the cell nucleus, so they generate a weaker immune response than mRNA vaccines. However, once the plasmid DNA enters the nucleus, it can produce several copies of the mRNA, which produces more antigen than a single molecule of mRNA. Additionally, DNA vaccines also carry the potential risk of insertional mutagenesis, whereas mRNA does not have the risk of insertional and integration into the genome.

5.4. DNA vaccines

Cancer DNA vaccines are based on bacterial plasmids that encode one or more cancer antigens that induce activation of the innate and adaptive immune responses. Answer [27]. In 1990, Wolf et al. Naked DNA was injected directly into mouse muscle to observe the expression of the corresponding protein.[14] The first human trials of a DNA vaccine to treat immunodeficiency virus type 1 (HIV) were reported in 1998.[14] We have been studying DNA for a long time and results are still limited. Until recently, India Approved COVVI-19 DNA vaccine.(ZycoV-D) was the first DNA vaccine approved for human use, marking the emergence of DNA vaccines for a range of diseases. DNA vaccines induce

humoral and cellular immune responses. DNA -vaccines must be entered After being transferred Antigen coded by cytoplasm. These antigens are treated and represented by CD8 + T and CD4 + cells Activates specification by MHC I and MHC II molecules Immune response. Mechanism of action of DNA vaccines They can be divided into three categories [12]: DNA hit Injected directly into body cells, such as muscle cells. Rear The antigen coded by translation and DNA is delivered directly to CD8 +cell poisonous T lymphocytes by MHC-1 molecule. You The second method is the antigen coded by the DNA Share cells are released by secretion or apoptosis. These peptides are phagocytosed, processed by APCs, and cross-presented by MHC II molecules to CD4+ T cells. The third pathway is direct transfection of DNA into APCs. Endogenous antigens produced by APCs are processed and presented to CD8+ and CD4+ T cells by MHC I and MHC II, respectively (28). Activation CD4+ T lymphocytes induce humoral immunity. CD8+ T cells Differentiate into CTLs and induce cellular immunity. Direct transfection of DNA plasmids into APCs Intradermal administration is considered the most important route for DNA vaccines against cancer [15]. In addition, CpG motifs in plasmid DNA help activate the innate immune response. CpG motifs can interact with TLR9 as a danger signal. TLR9 triggers a signalling cascade that activates NF-κB, IRAK and causes production of inflammatory chemokines and cytokines [28]. Double-stranded structures of DNA also activate STING signalling channel. STING is the primary DNA sensor that controls a cascade of cytoplasmic DNA signals Thus, DNA vaccines are not independent of TLRs. Induces strong adaptive immune responses in STING-deficient mice (17). DNA vaccines can encode multiple antigens or large antigens. DNA vaccines have high specificity and safety, low production costs, and are easy to transport and store. The insertional mutation rate of DNA vaccines is lower than the spontaneous mutations rate and the DNA rarely binds to host chromosomes

.Furthermore, the tumour antigen expressed by DNA cancer vaccines has the same species modification as the natural tumour antigen. DNA cancer Vaccines have specific advantages and optimized DNA Vaccines have proven that efficacy in preclinical models [15]. However, DNA-Vaccines has only reached minor progress in the clinical trials of their bad immunogenicity [28].

5.5. mRNA vaccines

The FDA recently approved two mRNA vaccines against COVID-19: Moderna's Spikevax and Pfizer's BNT162b2. BNT162b2 is also the first mRNA vaccine approved for sale by the FDA. Due to the advantages of mRNA vaccines in rapidly responding to the COVID-19 pandemic, the market value of mRNA vaccines has risen dramatically. Currently, CureVac, BioNTech and Moderna are the pioneers and leaders in the field of in vitro transcribed (IVT) mRNA vaccines. mRNA vaccines are a promising cancer vaccine platform in which exogenous synthetic mRNA is introduced into cells to provide a template for antigen synthesis, and the expressed antigens are delivered to the surface of APCs via MHC molecules to activate antitumor immunity. In 1990, scientists were successful In vivo, Lucifer, beta-galactosidase, Chloramphenicol Acetyl Transferase expressed MRNA. [29] with the vaccine. jirikowski discovered the MRNA Coding of oxytocin and vasopressin, which have been introduced in diabetes, can observe temporary changes. Diabetes insipidus within a few hours after injection 1992 [16]. Currently, mRNA cancer vaccines have shown promising clinical results in the treatment of various solid tumours [15]. What has further been found is that mRNA vaccines may improve the efficacy of other vaccine treatments. For example, mRNA vaccines encoding chimeric receptors targeting CLDN6, expressed in some solid cancer cells, have been shown to enhance the efficacy of claudin-CAR-T cells against solid tumours [29]. mRNA vaccines are mainly divided into non-replicating mRNA and self-amplifying RNA (SAM). MRNA, which has no repetitive position, is composed of 7-methylganosine (M7G) 5 '. CAP, 5'- tontransled area (5'-uUTR), open reading framework (OF), Cleaning Region 3 '(3'-UUTR) and 3'Poly (A) Tail [13]. TSE elements are important for MRNA's stability and series of transcription factors. Effective protein translation. 5' cap and 3' poly(A) tails can be enzymatically added after the first IVT. In contrast to mRNA is not replaced and SAM has two OFRs. One encodes objective antigen, and another encodes viral replication component, enabling long-lasting RNA amplification in cells. SAM is originated from alphavirus, and it replicates and magnifies in vivo to induce a persistent and efficient immune response. SAM allows the administration of small doses of vaccines while producing large amounts of antigen over a period of time. However, demand is high SAM in cancer vaccines is still in the preclinical stage and its clinical application requires further research [30]. mRNA cancer vaccines rarely replicate [19, 10]. Therefore, we focus primarily on non-replicating mRNAs.

6. Conclusion

The development of cancer vaccines is an important breakthrough in the treatment of solid tumours. In this review, we summarize the mechanisms of action, optimization strategies, and clinical progress of cancer vaccines, which are expected to facilitate the future development of cancer vaccines. Vaccines. In addition, we highlighted: Barriers to the application of cancer vaccines Therefore, we offer combination therapies for tumour resistance. Improve clinical

efficacy. Thanks to the advances in our understanding of immunological mechanisms and sequencing technologies, personalized cancer vaccines can be developed rapidly. Customized neoantigens Can induce true tumour-specific T cell responses. Central immune tolerance is limited. However, by eliminating tumour cells expressing specific neoantigens, they can inhibit tumour cell proliferation without neoantigens [30]. Targeting multiple neoantigens in a single vaccine May be a way to reduce immune evasion and effectively eliminate tumours. Highly effective neoantigens This needs to be further predicted and identified, but currently, some neoantigens may induce effective antitumor immune responses. In addition, the subjects of therapeutic trials of cancer vaccines are mainly patients with tumours in whom traditional treatments have failed and the disease has progressed. Theoretically, cancer vaccine therapy is more suitable for patients with a complete immune system, a lower tumour burden, and a higher risk of relapse. Therefore, future cancer vaccine clinical trials should take into full consideration the function of the patient's immune system and tumour burden. In conclusion, cancer vaccines are promising immunotherapeutic agents to stimulate the immune system to kill tumours and establish immune surveillance. However, much remains to be done to identify neoantigens, develop combination therapies, and optimize vaccine platforms before cancer vaccines become an effective strategy in immunotherapy.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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