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Covid-19 Vaccines: DNA Developing Immuno-Therapeutics Strategies against Cancer and Current Progress

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Abstract

Research on tumor 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 tumors. Cancer vaccine stimulates anti-tumor immunity with tumor antigens, which could be delivered in the form of whole cells, peptides, nucleic acids, etc. Ideal cancer vaccines could overcome the immune suppression in tumors and induce both humoral immunity and cellular immunity. In this review, we introduced the working mechanism of cancer vaccines and summarized four platforms for cancer vaccine development. We also highlighted the clinical research progress of the cancer vaccines, especially focusing on their clinical application and therapeutic efficacy, which might hopefully facilitate the future design of the cancer vaccine.

Introduction

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. As the vaccine developed, it was later introduced to treat more diseases, such as cancers. The initial cancer vaccine based on tumor cells and tumor lysates was developed in 1980. Scientists used autologous tumor cells to treat colorectal cancer. In the early 1990s, the first human tumor antigen melanoma-associated antigen 1 was identified, which opened a chapter on using tumor antigens in cancer vaccines. In 2010, a dendritic cell-based vaccine was successfully used to treat prostate cancer, proving the viability of cancer vaccines and creating great excitement in the cancer vaccines field [1]. 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 tumor-associated antigens (TAAs) and tumor-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 tumor growth and ultimately eradicate tumor cells. Currently, most cancer vaccines are still in the stage of preclinical and clinical research. More specific antigens and vaccine development platforms need to be developed [2].

The treatment purposes, which aim to kill tumor cells via tumor antigen-specific cellular immune responses, make cancer vaccines different from traditional vaccines. Only two FDA-approved prophylactic vaccines have been applied to prevent malignancies caused by viruses by now (Hepatitis B virus and human papillomavirus). Moreover, unlike traditional vaccines with antigens from foreign pathogens, tumor antigens are endogenous with low immunogenicity. Tumor antigens are often difficult to elicit an effective immune response. Furthermore, traditional vaccines induce humoral immunity. However, $CD8^+$ cytotoxic T cell-mediated cellular immunity is crucial in eliminating malignant cells for cancer vaccines [3].

Based on the different preparation methods, platforms for cancer vaccines are divided into four categories: cell-based vaccines, viruses-based vaccines, peptide-based vaccines, and nucleic acids-based vaccines. Vaccines that use whole cells as antigen carriers are called cell-based cancer vaccines. Cell-based vaccines are the main form of primeval cancer vaccines, where dendritic cells (DCs) vaccine has achieved significant results in clinical trials. Virus-based cancer vaccines mainly use viruses as vectors to treat and prevent tumors. Peptide-based vaccines are composed of known or predicted tumor antigen epitopes [4]. Peptide-based vaccines are often less immunogenic, requiring a combination with adjuvants to enhance their immunogenicity. Nucleic acid vaccines include DNA and RNA vaccines, composed of the encoding gene and carrier group of pathogen antigens. DNA cancer vaccines are closed circular DNA plasmids encoding TAAs or immune modulatory molecules to induce tumor-specific responses. mRNA vaccines are synthesized in vitro; they could encode antigens and express proteins following internalization to stimulate an immune response. In recent years, combining cancer vaccines with various immunotherapies or standardized treatments has become an effective strategy for overcoming tumor resistance and improving clinical outcomes [5].

Cancer vaccines have been intensively studied over the past decade. The availability and low cost of high-throughput sequencing technologies have led to the identification of numerous tumor neoantigens. The in-depth study of immunological mechanisms and various new vaccine platforms have extensively promoted cancer vaccines research. In this review, we introduced the working mechanism of cancer vaccines and summarized four platforms for the development of cancer vaccines. We also highlighted the research progress of the cancer vaccine, especially focusing on their clinical application and therapeutic efficacy, which might hopefully facilitate the future design of the cancer vaccine [6].

Cancer antigens

Scientists have identified a large number of cancer-associated antigens, many of which are now being used to perform cancer treatment vaccines both in basic research and in clinical trials. The list

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of candidate tumor antigens grows daily, largely because of expanding genetic technology including human genome sequencing and gene-expression profiling. Tumor antigens have been classified into two broad categories: tumor-specific shared antigens and tumor-specific unique antigens. Unique tumor antigens result from mutations induced through physical or chemical carcinogens; they are therefore expressed only by individual tumors [7]. Optimally designed cancer vaccines should combine the best tumor antigens with the most effective immunotherapy agents and delivery strategies to achieve positive clinical results. An important dilemma for vaccination against overexpressed tumor-associated antigens is how to induce effective immunity against the chosen target without leading to damaging autoimmunity. The precision offered by DNA vaccines will induce focused immunity against selected antigens, and, as they become more powerful, targets will have to be selected carefully to avoid autoimmunity. Recently, an NCI pilot prioritization study produced a well-vetted, priority-ranked list of cancer antigens. Antigen prioritization involved developing a list of "ideal" cancer antigen criteria/characteristics and assigning relative weights to those criteria using pairwise comparisons. The result of criteria weighting was as follows: (a) therapeutic function, (b) immunogenicity, (c) role of the antigen in oncogenicity, (d) specificity, (e) expression level and percent of antigen-positive cells, (f) stem cell expression, (g) number of patients with antigen-positive cancers, (h) number of antigenic epitopes, and (i) cellular location of antigen expression. Such an effort to prioritize cancer antigens represents the logical next step in attempting to focus translational efforts on cancer vaccine regimens with the highest potential for success. A biological issue limiting the efficacy of cancer vaccines is the low immunogenicity of cancer antigens. Strategies to enhance antigen immunogenicity are discussed in a later section [8].

Virus-based cancer vaccines

One of the primary benefits of virus-based vaccines is that the vaccine can make innate and adaptive immune work together to achieve an effective and long-lasting immune response. The virus-based vaccine can be divided into three forms: inactivated, live attenuated, or subunit vaccines against the virus that can cause the tumor; the oncolytic virus vaccine and the virus vector vaccine. It was reported that about 12% of cancer is attributed to viral infections. Epstein-Barr virus, HBV, Hepatitis C virus, and HPV are the most common cancer-related viruses. Inactivated whole virus vaccines have shown promising efficacy in treating Covid-19 or Ebola. Logically, it would show the same effectiveness in treating virus-related cancer. However, it was used less frequently in oncological diseases, probably because of difficulties in production and safety issues. Instead, with the development of bioengineering technology, the approach like virus-like particle is increasingly used in the treatment [9].

Oncolytic virus is a novel immunotherapy that explicitly kills tumor cells and promotes anti-tumor responses. After being infected by the oncolytic virus, tumor cells produce ROS and cytokines, stimulating immune cells. Subsequently, the oncolysis would happen, and substances like TAAs would release as well. The anti-tumor efficacy of oncolytic viruses has already been proved in various clinical trials. The sorts of oncolytic virus contain herpes simplex virus, adenovirus, measles, vaccinia, reovirus, vesicular stomatitis virus, etc. Among them, T-VEC, a first-generation recombinant herpes simplex virus product, has been the most striking one so far. In addition to the herpes simplex virus, the adenovirus is another commonly used oncolytic virus, which is frequently used as delivery vectors for specific genes as well. Adenovirus is easy to manipulate, its gene structure is clear, and it is easy to achieve gene transfer and tumor antigen expression [10]. Second, adenoviruses have a very broad spectrum of host cell tropism and can be rapidly 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 cancer vaccines, both as non-replicating vectors and oncolytic adenoviruses, have shown promise in preclinical and clinical trials. Except for adenovirus, other vectors like vaccinia virus, lentivirus adeno-associated virus are also used on the tumor vaccine platform, in which lentivirus and adeno-associated virus have the unique ability to stably and long-termly express the transgene in non-dividing cells the same as adenovirus.

Optimization strategy for virus-based cancer vaccines

Improving TME is a viable strategy to optimize the efficacy of virus-based vaccines. With the increasing knowledge on the mechanisms of immunosuppression in TME, various strategies combined with viral vaccines have become feasible. Combining virus-based vaccines with PD-1 inhibitors is the most common. The vaccination of virus vaccine combination with PD1 blockade showed a long-term tumor-free survival in the tumor model. Except for combining with checkpoint inhibitors, other potential ways should be concerned. Widely studied protein YAP, a coactivator of the Hippo pathway, was found to do with Treg regulation, which is a significant immunosuppressive cell.

In addition to combination therapy, virus-based vaccines are also designed to express immune-regulating molecules to disrupt TME. Patients receiving TG4010, a therapeutic viral vaccine encodes human mucin-1 and interleukin 2, have shown a longer median survival period. BT-001, another oncolytic virus vaccine, which could express anti-CTLA4 antibody and granulocyte macrophage colony stimulating factor, is worthy of being concentrated on. It has already been tested in a clinical trial [11]. Besides, other strategies like the fusion-enhanced oncolytic immunotherapies based on the simplex virus, as well as the combination of virus-based vaccine to chemotherapy, adoptive T cell therapy and radiation therapy, are being further tied. The antiviral immune response neutralizing the viral vector needs to be avoided for the virus vectors vaccine. Heterogeneous priming and enhancement strategies mean using one viral vector to deliver the antigen and then using different types of viral vectors to deliver the same tumor antigen for enhancement.

DNA vaccine

Cancer DNA vaccines are based on bacterial plasmids that encode one or several oncology antigens inducing innate immunity activation and adaptive immune responses. As early as 1990, Wolff et al. directly injected naked DNA into murine muscle and observed the expression of corresponding proteins. Although we have been studying DNA vaccines for a long time, there are still limited results. Until recently, India approved a COVID-19 DNA vaccine. ZycoV-D was approved as the world's first DNA vaccine for humans, heralding the arrival of DNA vaccines for various diseases.

DNA vaccines induce both humoral and cellular immune responses. DNA vaccines need to enter the nucleus to be transcribed and then translated to the encoded antigens in the cytoplasm. The antigen is processed and presented to CD8+ T and CD4+ T cells by MHC I and MHC II molecules to activate specific immune responses. The action modes of DNA vaccines can be divided into three categories. DNA goes directly into a somatic cell, such as a muscle cell. After translation, the DNA-encoded antigens are directly delivered to cytotoxic CD8+T cells by MHC-1 molecules. The second pathway is that the antigen encoded by DNA in somatic cells is released by secreting or apoptotic bodies. These peptides are phagocytosed, processed by APCs and cross-

presented by MHC II molecules to CD4+ T cells. The third pathway is directly transfecting DNA into APCs. The endogenous antigens produced by APCs are processed and presented to CD8+ T and CD4+ T cells by MHC I and MHC II, respectively. The activation of CD4+ T cells induces humoral immunity. CD8+ T cells are differentiated into CTLs to induce cellular immunity. Direct transfection of DNA plasmids into APCs, mainly through intradermal delivery, is considered the most critical pathway for DNA cancer vaccines [12].

Moreover, CpG motifs in plasmid DNA help activate innate immune responses. CpG motifs can interact with TLR9 as a danger signal. TLR9 triggers a signaling cascade that activates NF-κB, IRAK and elicits the production of chemokines and inflammatory cytokines. DNA double-stranded structure also activates the STING signaling pathway. STING is a primary DNA sensor that controls the cascade of cytoplasmic DNA signals independent of TLR, which is why DNA vaccines did not produce a robust adaptive immune response in STING deficient mice. DNA vaccines can encode multiple antigens or large antigens [13]. DNA vaccines are highly specific and safe, with lower production costs and they are facile 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 tumor antigen expressed by DNA cancer vaccines has the same species modification as the natural tumor antigen. DNA cancer vaccines have particular advantages, and optimized DNA vaccines have proven efficacy in preclinical models. However, DNA vaccines have only achieved minor progress in clinical trials due to their poor immunogenicity.

Conclusions

The development of cancer vaccines is an important breakthrough in treating solid tumors. In this review, we have summarized the working mechanisms, optimization strategies, and clinical progress of cancer vaccines, which might hopefully facilitate the future design of the cancer vaccines. In addition, we also highlighted the existing barriers for the cancer vaccine translation, such as tumor resistance, therefore, proposing a combination therapy to improve the clinical efficacy. With further understanding of the immunological mechanisms and sequencing technology development, personalized cancer vaccines might be rapidly developed. Personalized neoantigens could elicit an actual tumor-specific T cell response with limited central immune tolerance. However, eliminating tumor cells expressing a specific neoantigen lead to the outgrowth of tumor cells without the neoantigen. Targeting multiple neoantigens within a single vaccine might be a direction to reduce immune evasion and effectively eliminate tumors. Highly effective neoantigens need to be further predicted and identified for that only a few neoantigens could induce effective anti-tumor-immune responses currently.

Additionally, the therapeutic trial objects of cancer vaccines are mainly tumor patients who have failed traditional treatment methods and progressed. Theoretically, cancer vaccine therapy is more suitable for patients with a complete immune system, a smaller tumor load and a greater risk of recurrence. Therefore, future clinical trials of cancer vaccines should fully consider the patient's immune system function and tumor burden. In conclusion, cancer vaccines are promising immune-therapeutics for stimulating immune system to kill tumors and establishing immune surveillance. However, much work remains to be done on identifying neoantigens, developing combination therapy, and optimizing vaccine platforms before cancer vaccines become a potent strategy in immunotherapy.

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