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Vaccine Therapies for Cancer: Challenges and Strategies

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Abstract. As oncology vaccines have become more effective in clinical trials, it has become clear that they have great potential to attack malignant tumors in the future. Even though oncology vaccines are now a minor success and most of the cancer vaccines in the market are prophylactic rather than therapeutic for malignant tumors, cancer vaccines are still in the limelight and a lot of research has been invested in this area. From the time that tumor vaccines were noticed and researched to the present day, they have always faced difficulties, which has led to no breakthrough in cancer vaccines for a long time. Nowadays, only a small percentage of cancer vaccines have been put into clinical use despite the tireless efforts of people. There is still a lot of room for progress in cancer vaccines, and this paper goes through the development, types, and mechanisms of cancer vaccines to understand the advantages and disadvantages of cancer vaccines and analyze the challenges and strategies of cancer vaccines.

Keywords: Vaccines, cancer therapies, tumor antigen.

1. Introduction

Cancer is becoming progressively globalized and widespread. Because of the influence of the social environment people, inflation, economic pressure, life pressure, psychological pressure, and social pressure gradually become the main problems faced by people. Stress leads to irregular work and rest, and an irregular diet can lead to increased chances of cancer. In 2019, about 10 million people died because of cancer [1]. Therefore, cancer treatment has gradually become one of the most critical approaches in medicine, and doctors have invented chemotherapy, transplantation, gene cutting, CRISPR, and other ways to treat cancer. However, with the emergence of the first vaccine to treat cancer, doctors have begun to pay more attention to the application of vaccines in cancer. Compared to common cancer treatments, such as radiation therapy, this treatment can affect the patient's physical condition, and even if the cancer recovers, irreversible side effects may occur. The treatment period is long, the patient suffers during the treatment, the recovery is slow, and there may be side effects, but compared to cancer vaccines, cancer vaccines have a shorter treatment period, and they also reduce the patient's suffering as well as reduce the risk of side effects. Especially for some of the more common cancers, the emergence of cancer vaccines can reduce people's suffering and can be used to treat and prevent common diseases. Cancer vaccines were first developed in the 19th century, after which vaccines were invented for both hematologic and solid tumors but have not been developed with more recent success. In the early days, due to the advent of smallpox vaccines to stop people from getting sick with smallpox and thus gaining immunity to smallpox, this review systematically the history and mechanism of cancer vaccines, as well as discusses the challenges and strategies of cancer vaccines.

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2. Cancer Vaccines

2.1. Cancer vaccine types

Cancer vaccines are a form of immunotherapy, similar to the role of vaccines in prevention. Cancer vaccines allow the immune system to understand and recognize cancer cells so that it can destroy them. However, cancer vaccines are much more complex than regular vaccines. The ordinary vaccines we use in the market usually prevent viruses and bacteria, such as inactivated, attenuated, and recombinant vaccines, etc. Either of these vaccines is designed to allow the immune system to recognize the virus or bacteria in advance for preventive purposes. Just go ahead and extract the virus or bacteria and process it. But cancer vaccines are not so simple. Cancer cells are more similar to the cells present in the body itself than bacteria and viruses, which makes it more difficult for the immune system to recognize them. On the flip side, each person's cells are different, and each person's situation and cancer cells are different. As a result, cancer cells have different antigens, which also leads to the fact that if an effective vaccine is to be developed and a cancer vaccine that can be put into clinical use, it will be much more difficult than one would normally imagine.

Preventive cancer vaccines, as the name suggests, are used to prevent cancer, such as human papillomavirus (HPV). The availability of the HPV vaccine has greatly reduced the likelihood of cervical cancer and it is available to both men and women. Moreover, the HPV vaccine protects women of different ages, so even if this woman is 30-40 years old, there is an HPV vaccine that is best suited for her. In addition, Hepatitis B Virus (HBV) can cause liver cancer, and both cancers can now be prevented with vaccines.

Therapeutic cancer vaccines are cancer vaccines that specifically target malignant cancers. Since everyone's antibodies are different, which is what makes therapeutic cancer so difficult, doctors and physicians are now able to differentiate between normal and cancerous cells through targets, and by using and analyzing the targets, the sipuleucel-T vaccine was invented. This vaccine can be administered through dendritic cells, and by using the patient's own cellular makeup, the sipuleucel-T vaccine can now be applied to advanced prostate cancer. This vaccine was developed by looking at the targets on the patient's tumor, which in turn revealed overexpression of some of the proteins, and it was found that this property could be used for the treatment of malignant tumors.

BCG is a vaccine against tuberculosis that China requires every child to receive within 24 hours of birth to prevent tuberculous meningitis. BCG was approved in the United States as early as 1990 and is now also used to treat early-stage bladder cancer. It is an attenuated vaccine, thus stimulating feedback from the immune system.

Personalized neoantigen vaccines are based on a unique target created by a mutation in the cancer that produces a new antigen. Cancer cells express this target while normal cells do not, thus protecting normal cells from attack and reducing side effects on patients [2].

2.2. The mechanism of vaccines

Cancer vaccines stimulate the immune system by recognizing proteins known as antigens. There are several ways in which the recognition proteins can activate the immune system to achieve therapeutic effects. The first of these is the delivery of the recognition protein to the immune cells in the dendritic cells. The first way is to deliver an identifying protein from several patients with the same type of cancer. The second way is to use messenger mRNAs to generate unique neoantigens for individual cancers and to inject prepared identifying proteins into the dendritic cells or to allow the antigen to be taken up by the dendritic cells in the body [3].

The most important aspect of a cancer vaccine is the choice of antigen. Ideally, a cancer antigen should be able to be expressed in all cancer cells without affecting normal cells and should be highly immunogenic. The most useful and critical tumor antigen today is the T-lymphocyte recognition protein, which is also the most central and important protein. Regarding cancer vaccines, antigens can be divided into two types: tumor-associated antigens (TAA) and tumor-specific antigens (TSA) (figure 1).

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TAA is further divided into two types: one is coming from autoantigens, and the other is non-autoantigens. Where autoantigen denotes something like differentiation antigen, etc., and TSA denotes antigens from viruses [4].TAA antigens are highly expressed in tumor cells and are also present in healthy cells, even at low levels of expression; in contrast to TAA antigens, TSA antigens are specific to cancer cells and are not present in healthy cells [5]. Tumor-associated antigens (TAA) can be found in any protein or glycoprotein synthesized in the tumor cell, and this protein may be cytoplasmic, membrane-bound, nuclear, or secreted by the tumor cell itself. There are differences in the expression of TAA, preferentially allowing specific T-cells or immunoglobulins to carry out the tumor cells' recognition. TAA is mainly derived from gene amplification or post-translational modification and tends to be highly or characteristically expressed in tumor cells [6].

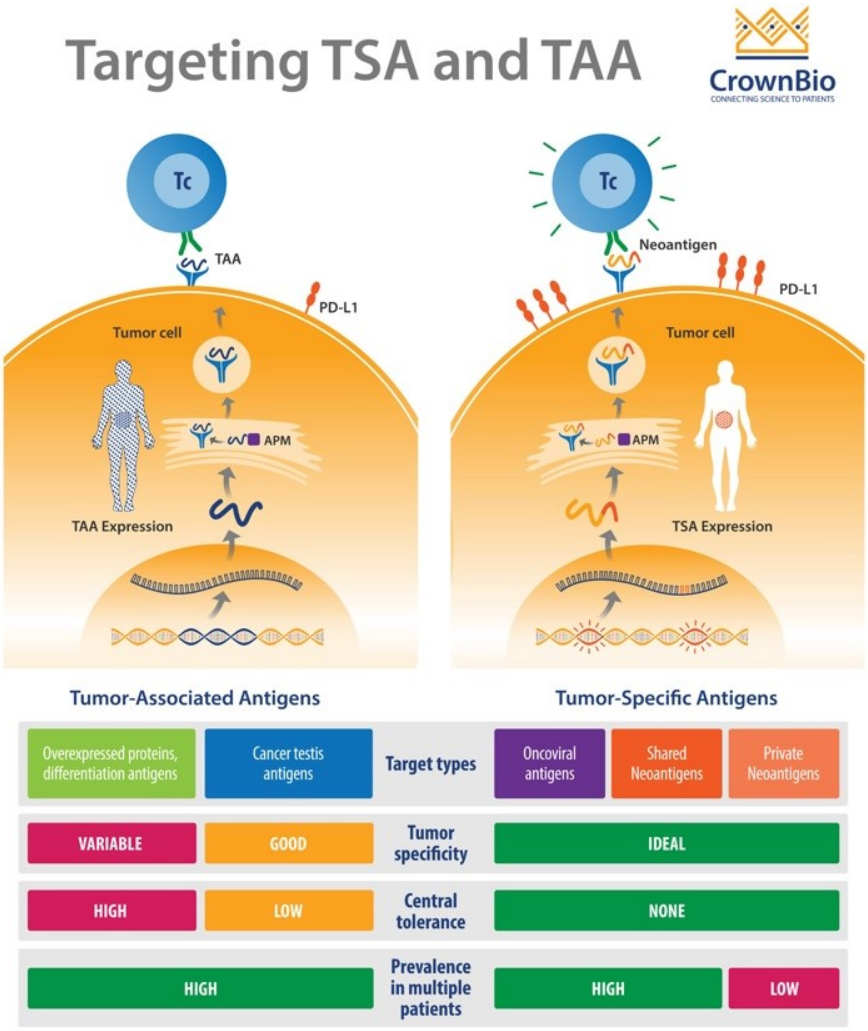

Figure 1. The difference between TSA and TAA [5].

TAA is adaptive, which means that TAA can be applied to more than one patient and can be applied to different patients. Although early cancer vaccines were more focused on TAA, this also leads to the fact that the efficacy of the vaccine will be compromised because of the immunological tolerance of the thymic centres since the T cells recognizing the TAA or self-antigens may be lost. So, the main problem with TAA now is tolerance, and although TAA has been on the radar for a long time, there has still not been a breakthrough on this issue. Also, TAA in non-malignant tissues enhances the toxicity caused by the overreaction of the autoimmune system after vaccination.

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TSA is mainly derived from the production of new peptide sequences (i.e., neoantigens) by mutation driven by carcinogenesis and can also be induced by oncogenic viruses, such as alpha-fetoprotein (AFP)-expressed in germ cell tumors and hepatocellular carcinomas. This neoantigen is expressed only in tumor cells and can induce an effective tumor-specific T-cell response. Compared to TAA, the neoantigen has a higher immunogenicity and is more compatible with the histocompatibility complex (MHC). They are not affected by central immunity, i.e., there is no need to consider central tolerance. Neoantigens are becoming more likely in the future and are becoming predictable in the development of cancer vaccines for humans. Another development regarding MHC class I binding epitopes also makes potential new immunogenic epitopes a more important target. There are also several neoantigens that have shown promising results in clinical trials, which could improve the survival rate of cancer patients with malignant tumors in the future [4].

3. Current types of cancer vaccines

3.1. DNA vaccines

DNA cancer vaccine is a vaccine based on DNA technology that is used to prevent or treat cancer. It activates the human immune system to recognize and attack cancer cells by introducing plasmid DNA encoding specific tumor antigens. Its working principle is to inject plasmid DNA encoding tumor antigens into the human body, and human cells absorb these DNAs and express corresponding antigenic proteins. These antigenic proteins are recognized by the immune system, thereby activating specific immune responses to attack and eliminate cancer cells carrying these antigens. The rapid screening of antigens and the construction of particular types of constructs make DNA vaccines a field worth exploring.

The effectiveness of rapid screening of antigens and the design of specific types of expression constructs make DNA vaccine research a valuable field for cancer immunotherapy. DNA vaccines provide the opportunity to integrate gene coding. There are several ways to deliver these gene sequences, such as delivering them to the subcutaneous, skin, or muscle. The plasmid enters the nucleus of some local cells through the host cell, and then the plasmid gene can be expressed. DNA vaccines allow the introduction of many immunizing components and modification by PCR and synthesis. DNA vaccines have a relatively low immunogenicity, and in experiments, attempts have been made to elicit the immune response produced by DNA vaccines, but in the end, only by using very high concentrations of DNA was it possible to achieve the right amount of immunogenicity. In clinical trials, DNA vaccines have not been able to achieve an immune response, although progress has been made in modifying the DNA [7].

3.2. RNA vaccines

In recent years, mRNA vaccines have continuously acquired clinical data and have begun to be put into human clinical trials. mRNA cancer vaccines are vaccines that use mRNA technology to prevent or treat cancer. This vaccine activates the human immune system to recognize and attack cancer cells by introducing mRNA encoding specific tumor antigens. mRNA encoding specific tumor antigens is injected into the human body. Human cells absorb these mRNAs and synthesize corresponding tumor antigen proteins according to their instructions. These antigen proteins are recognized by the immune system and activate specific immune responses against tumors, including humoral immunity (antibody production) and cellular immunity (T-cell response). By introducing a segment of mRNA corresponding to a segment of viral protein, it generally refers to the protein on the outer membrane of the virus. Among them, TAA and TSA in 2.1 are representatives of RNA vaccines [8]. As shown in figure.2, the first step of designing mRNA is sample acquisition. To collect the tumor tissues and normal tissue, genome-wide sequencing and targeting identification are used to identify the genome. After that, it can used to do the mRNA cancer vaccine design and production. At last, it will try until it can used in the human body.

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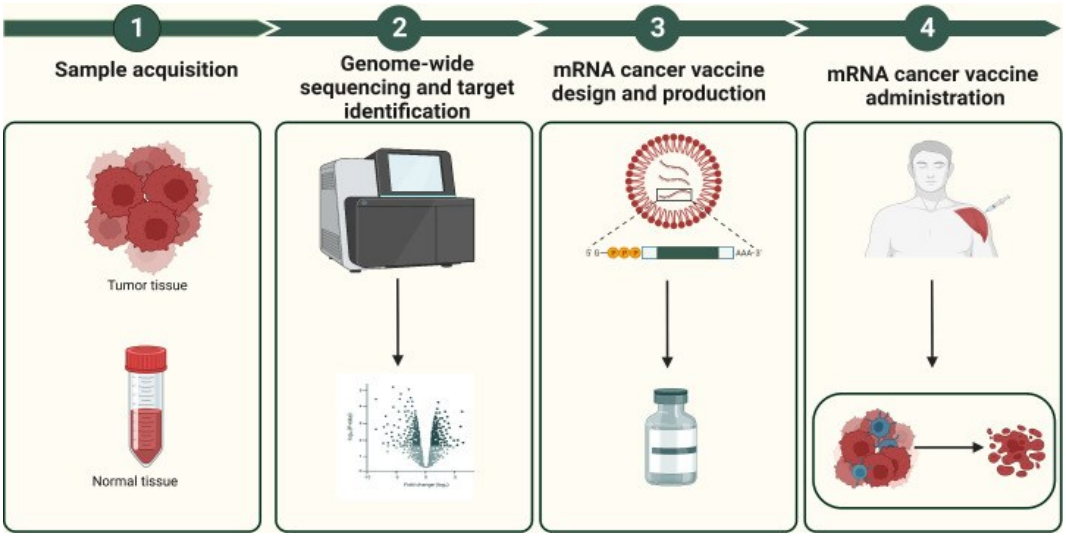

Figure 2. How mRNA was designed and produced [8].

3.3. Proteins or synthetic peptides of tumor antigens

Cancer vaccines based on proteins or synthetic peptides of tumor antigens are a type of treatment that activates the body's immune system to recognize and attack cancer cells by introducing specific tumor antigens. These tumor antigens can be proteins naturally present in cancer cells or peptide fragments made through synthetic technology. Researchers identify unique tumor antigens expressed in specific cancer types. These antigens are usually expressed at low levels or not present in normal cells. Antigen-presenting cells in the immune system (such as dendritic cells) recognize and process these tumor antigens and present them to T cells, which are activated to specifically recognize and attack cancer cells that express the same tumor antigens.

Tumor-associated macrophage (TAM) This is a very efficient cell type that can tackle cancer cells with fewer restrictions than other cells. But TAM can release different cells, especially in the tumor environment, and can release multiple factors that allow cancer cells to divide and spread. So there are two states of TAM, anti-tumor M1 and protumor M2, both of which can be used to manage the spread and address the cancer. So, TAM is now becoming an important therapeutic target in cancer immunotherapy. Regarding peptide cancers, it is possible to use macrophages for therapeutic modalities. This, especially M2-TAMs, can now be used as an intermediate bridge for potent therapeutic drugs by targeting M2-TAMs, and cut can show tumor activity. In this way, the signalling of cancer cells can be blocked. For example, melanoma tumors [9].

3.4. Cell-based delivery of cancer vaccine development

This is a cell-delivered cancer vaccine, a cancer treatment method that uses cells as carriers to deliver tumor antigens to the immune system, thereby activating a specific immune response. Dendritic cells (DC) are usually used as the main antigen-presenting cells, and other types of immune cells such as T cells or B cells can also be used. Tumor antigens (such as tumor cell extracts, peptides, proteins, or DNA/RNA) are loaded onto these immune cells.

These antigens can be added to cells by in vitro treatment or directly loaded with carrier cells in vivo. T cells recognize and are activated to produce a specific anti-tumor response. This response includes the direct killing of tumor cells and the generation of immune memory to respond to future tumor challenges.

This type of vaccine is more used for preventive tumor vaccines, such as HPV and HBV. This vaccine is not only obviously helpful in preventing early tumors, but also protects high-risk individuals and shows potential in fighting liver cancer. For example, the DNA vaccine of B cells, GRP18-27, can prevent liver cancer. Another example is attenuated live Listeria, which can also be used as a vaccine

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and is very safe. This vaccine has shown great results in the liver, such as liver fibrosis, hepatobiliary malignancies, etc. [10].

4. The challenges and strategies of cancer vaccine development

4.1. Advantages and strategies of cancer vaccines

Taking mRNA cancer vaccines as an example, mRNA cancer vaccines have nine major advantages: rapid production, highly targeted, low production costs, fewer side effects, lower risk of insertional mutagenesis, support personalized therapy, lower risk of viral infection, induce stronger immune responses and short research and development cycle. Compared with common treatment options, such as chemotherapy, transplantation, surgery, etc., which require the patient to consume himself or have a greater physical impact on the patient, cancer vaccines can reduce the patient's pain, reduce the occurrence of side effects, and allow patients to recover faster, especially for malignant cancers. At the same time, it can prevent cancer from recurring to a greater extent and reduce the probability of patients having the same problem again after recovery. When choosing cancer vaccines, it is necessary to choose the right antigens, the right adjuvants, and the right delivery system, which can increase the effectiveness of cancer vaccines and reduce the probability of cancer vaccines being off-target [11].

4.2. Challenges of cancer vaccines

Up to now, cancer vaccines still face many challenges and problems. For example, the TAA mentioned above has the problem of drug resistance. Tumors do not express foreign antigens. Many new antigens may be generated due to tumor-specific mutations. Up to now, the cancer vaccines widely used and trusted by people are still not used to treat malignant tumors. Still, the human papillomavirus and hepatitis B virus vaccines mentioned above are more for preventing malignant tumors, not for treatment. Many cancers are unrelated to specific infectious diseases in a certain antigen. Still, they are caused by different environmental factors, genetic inheritance, lifestyle, and other similar factors of each person, which also affect the ability of this cancer vaccine. Tumors that can treat cancer have significant challenges for established tumors. Tumor target antigens will be overexpressed compared to normal tissues. Many of these antigens may be challenging to target antigens, or they may not be carcinogenic drivers, which may reduce the effectiveness of antigen-targeted vaccines or make it difficult to identify targets. The immune system of cancer patients operates in a different and unknown environment and faces more immune problems and

The immune system of cancer patients operates in a completely different environment, and compared with healthy individuals, it faces many challenges in driving immune responses [12].

5. Conclusion

Cancer vaccines leave a lot to be desired. Overall, DNA vaccines, RNA vaccines, proteins or synthetic peptides of tumor antigens, and cell-based delivery of cancer vaccine development are the types of cancer vaccines that have been developed so far in cancer vaccines. Although the majority of commercially available vaccines are still prophylactic vaccines, such as the HPV vaccine and the HBV vaccine, a number of vaccines targeting the treatment of malignant tumors have been put into use, such as Bacillus Calmette-Guérin (BCG) vaccines, personalized neoantigen vaccines, and so on. This shows that people are progressing, and there is more room for the development of cancer vaccines. Until now, cancer vaccines have more problems and side effects and need to consider different situations and factors such as drug resistance, body, environment, genes, etc., to analyze the antigen and targeting, which is also a challenge for cancer vaccines. Once these challenges and shortcomings are perfected and more detailed research is conducted, then more patients can be treated and more malignant tumors can be solved in the future, while the patients can reduce the side effects, risks, lower risk of viral infection, and reduce the rate of recurrence, and reduce the pain. This is extremely important for the development of modern medicine.

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References

[1] Saxena M, van der Burg SH, Melief CJM, Bhardwaj N. Therapeutic cancer vaccines. Nat Rev Cancer. 2021 Jun;21(6):360-378.
[2] Igarashi Y, Sasada T. Cancer Vaccines: Toward the Next Breakthrough in Cancer Immunotherapy. J Immunol Res. 2020 Nov 17;2020:5825401.
[3] Drew L. How does a cancer vaccine work? Nature. 2024 Mar;627(8005):S34-S35.
[4] Liu J, Fu M, Wang M, Wan D, Wei Y, Wei X. Cancer vaccines as promising immuno-therapeutics: platforms and current progress. J Hematol Oncol. 2022 Mar 18;15(1):28.
[5] Tumor-associated antigen (Taa) or tumor-specific antigen (TSA)-targeted therapy. Crown Bioscience. (n.d.). https://www.crownbio.cn/targeting-tumor-associated-antigens-and-tumor-specific-antigens/
[6] Zarour, H. M. (1970, January 1). Categories of tumor antigens. Holland-Frei Cancer Medicine. 6th edition. https://www.ncbi.nlm.nih.gov/books/NBK12961/
[7] Fioretti D, Iurescia S, Fazio VM, Rinaldi M. DNA vaccines: developing new strategies against cancer. J Biomed Biotechnol. 2010;2010:174378.
[8] Wang B, Pei J, Xu S, Liu J, Yu J. Recent advances in mRNA cancer vaccines: meeting challenges and embracing opportunities. Front Immunol. 2023 Sep 6;14:1246682.
[9] Zhang L, Huang Y, Lindstrom AR, Lin TY, Lam KS, Li Y. Peptide-based materials for cancer immunotherapy. Theranostics. 2019 Oct 15;9(25):7807-7825.
[10] Tojjari A, Saeed A, Singh M, Cavalcante L, Sahin IH, Saeed A. A Comprehensive Review on Cancer Vaccines and Vaccine Strategies in Hepatocellular Carcinoma. Vaccines (Basel). 2023 Aug 12;11(8):1357.
[11] Bowen WS, Svrivastava AK, Batra L, Barsoumian H, Shirwan H. Current challenges for cancer vaccine adjuvant development. Expert Rev Vaccines. 2018 Mar;17(3):207-215.
[12] Roser, M., & Ritchie, H. (2024, March). Cancer. Our World in Data. https://ourworldindata.org/cancer.