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Challenge and Solution for Cancer Vaccine Therapy for Breast Cancer

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Abstract. Although the development of targeted drugs has gained great success in cancer treatment, all metastatic cancers have developed resistance. All these therapies are no longer effective for about 33% of people with HER2-positive breast cancer. In vaccine treatment, antigens are delivered, interacting with cancer cells, and inducing a prolonged immune response. Effective vaccines can especially prevent cancer recurrence and defend against various tumor antigens since they have a longer immunological memory. Although there have been great advancements in cancer vaccine development over the past 10 years, there are still some major challenges to overcome. Combining adjuvants has considerably aided cancer vaccines in overcoming challenges such as tumor immunosuppression and antigenic immunogenicity. The benefits, drawbacks, and most recent developments of four breast cancer vaccinations are examined in this research. The result of the development of adjuvant techniques to circumvent low antigen immunogenicity and tumor immune evasion, which also can help the researchers to understand the molecular mechanisms behind these issues.

Keywords: cancer vaccine, breast cancer, adjuvant combination

1. Introduction

Cancer is a disease that starts uncontrollably anywhere in the human body. Cancer has a severe influence on society in the United States. Every year, a considerable number of people are diagnosed with cancer, and many people die. According to the cancer statistics from National Cancer Institute (NCI), in 2022, roughly 1.9 million people will be diagnosed with cancer in the U.S. About 28,785 women and 2,710 men are diagnosed with breast cancer, the most common cancer diagnosis case [1]. Also, in 2022, about 609,360 people will die because of cancer in the U.S, and 43,780 people will die due to breast cancer, which is the fourth most common cause of cancer [1]

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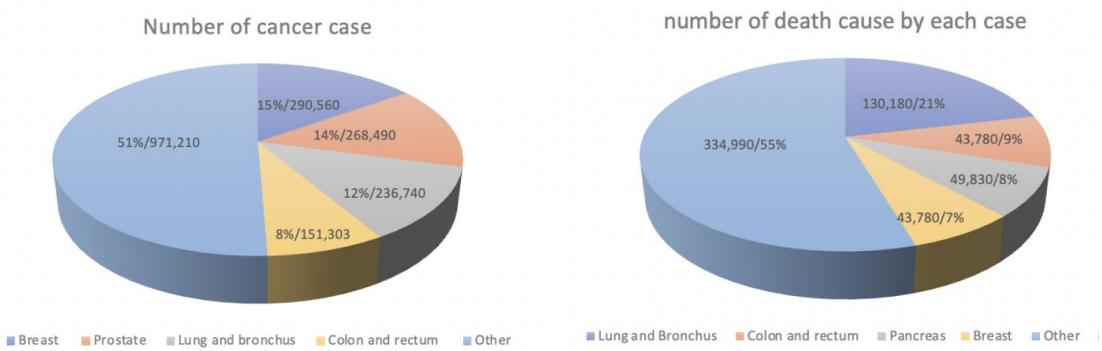

Figure 1. In 2022, new cancer cases and the number of cancer death in the United States.

Main glands, ducts, and fatty tissue make up the breast. Phyllodes tumors, angiosarcoma, lobular carcinoma, ductal cancer, and Paget disease of the breast all occur there. Cancer may be categorized into four subtypes based on the expression of hormones including estrogen and progesterone as well as the HER2 receptor: luminal A, luminal B, HER2-enriched, and basal-like triple-negative [2]. HER2-targeted treatments, such as trastuzumab, can currently be used to treat HER2-enriched breast cancer. The EGFR family includes the Human Epidermal Growth Factor Receptor 2 (HER2). Both HER2 positive and HER2 negative breast cancers contain elevated levels of HER2 [2]. Overexpressed HER2 connect with proliferation-related gene cluster, and HER2-positive breast cancer will cause a more severe prognosis and inferior outcome in survival [2].

The HER-2 gene is amplified, and protein overexpression is the cause of 10 to 34 percent of invasive breast cancer [3]. Amplifying the HER-2 gene in breast cancer will increase tumor invasiveness, tumor growth, and progressive local and distant metastases. Additionally, it will speed up angiogenesis and reduce apoptosis [3]. Surgery, radiation, hormone therapy, chemotherapy, and targeted therapies are now the recommended treatments for breast cancer. All of these therapies, meanwhile, come with unwanted side effects, such as weakness and exhaustion, hair loss, an increased risk of infection, and so forth. HER2 receptor-targeting monoclonal antibodies are a novel treatment with anti-tumor potential. The half-life of monoclonal antibodies restricts the length of therapy [4]. As a result, it becomes an appealing task to figure out how to create a vaccination that can cause a patient's immune system to respond long-term.

Cancer vaccination is a novel form of cancer treatment, and it contributes to the host immune response, which has an anti-tumor effect and has tremendous potential to overcome the innate resistance that restricts conventional cancer treatment. High specificity, minimal toxicity, and the potential for long-lasting therapeutic effects due to immunological memory are further benefits of cancer vaccines. In the past few years, cancer vaccines have made significant advances as more and more cancer antigens have been detected, the cost of in-depth research into the immune system has fallen, and antigen detection techniques have improved.

Cancer vaccines can be divided into two main categories: Preventive cancer vaccines and Therapeutic cancer vaccines. Cancer prevention can stop the viral infection from leading to cancer. Hepatitis B virus causes liver cancer, while the human papillomavirus (HPV) causes cervical, head, and neck cancer (HBV). The FDA has previously authorized four of these cancer vaccines for prevention. Cancer cells are difficult to identify from healthy cells. Therefore, more intricate cancer vaccination strategies are required to address this issue. Tumor cells from the normal cell can be the target of the therapeutic vaccination. The first therapeutic cancer vaccination authorized by the FDA was the sipuleucel-T vaccine. This vaccination seeks to target a typical protein that cancer cells make in excessively large amounts [5]. Therefore, the four primary cancer vaccine kinds and their processes will be covered in this article. Additionally, highlighting developments in cancer vaccine research with a focus on their clinical applicability and therapeutic efficacy may aid in the development of new cancer vaccines.

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2. Vaccine

Fully understanding the mechanism of the tumor environment, researchers gain s excellent achievements in the field of HER2-positive breast cancer. A cancer vaccine is an efficient treatment against tumor cells, including protein or peptide, DNA/RNA, whole cell, and dendritic cells[6]. HER2 protein already exists during the fetal period and can be found in the normal epithelial cells in adults [7]. So, human has some anti-HER2 immunity in their immune system. However, pre-exist anti-HER2 immunity is too low to trigger the anti-tumor response [7]. Therefore, Breast cancer vaccines are needed to build a strong and durable anti-tumor response.

2.1. Protein vaccine

Protein or peptide vaccine as a new cancer treatment including T cell-based and B cell-based has drawn much attention from researchers in the past few years. Protein or peptide vaccines provide many potential benefits to researchers and patients, including ease of production, lower cost, fewer side effects, and high chemical stability. However, the peptide cancer vaccine also has insufficient immunogenicity, so the appropriate adjuvant is needed to increase the efficacy [9].

The principle of the T cell-based cancer vaccine is conveying synthetic T cell epitopes into the body to trigger an immune response. Short peptide T cell would directly bind to histocompatibility complexity molecule I on all cells, which leads to trigger tolerance, not response on the immune system [4]. However, multivalent synthetic long peptides (SLPs) can activate CD+4 and CD+8 T cells [9]. SLPs can trigger a more efficient immune response. Since SLPs cannot directly bind to major histocompatibility complex (MHC) class I and their presentation to T cells, so they have to be taken up and processed before they are presented [10].

B cell peptide vaccine triggers the immune system through the B cell epitope of the tumor-specific antigen [2]. As a result, the downregulation of MHC-I as a tumor avoidance strategy does not affect how accessible an antibody's epitope is. The only way for a tumor to escape is through selection for antigen loss variants, although in the case of HER-2 and NEU, this has not frequently or never been seen. B cell epitopes are not constrained by HLA, enabling broad applicability in all HLA types [4]. T cell epitopes are constrained by HLA, which the creation of overlapping peptide constructions aims to address.

2.1.1. T-Cell peptide vaccine. Intradermal immunization reaching six times per month produced peptide-specific T-helper, CD8, and anti-HER-2 specific cellular immune responses, according to early clinical trials using T-helper peptides from ECD, ICD, and MHC Class I (or HLA-A2) binding domain restricted regions [11]. Kinetics investigations up to a year after the beginning of immunization have indicated that peptide-specific responses are elicited early, around two to four months after the beginning of immunization, but most patients need to finish a series of six vaccinations to establish HER-2 NEU-specific responses. The immunological response was maintained in 13% of these individuals for up to a year after the vaccination started [8].

2.1.2. B-CELL peptide vaccine. Patients had three monthly immunizations as part of the clinical trials for the B-cell peptide vaccine investigation. Small local adverse effects at the injection site were seen by a small number of subjects (4/10) who underwent the safety main objective, but no systemic side effects [4]. All but one of the patients exhibited HER-2/NEU antibody levels, and eight out of ten patients (8/10) showed anti-peptide antibody formation [4]. The number of Treg cells significantly decreased after vaccination, which may have a substantial effect on the effectiveness of the vaccine and the generation of a healthy immune response.

2.2. DNA/RNA vaccine

Immune responses are subsequently produced against cancer cells that express the tumor antigens (TAs) by the host after receiving genetic information encoding the TAs from DNA and mRNA vaccines [12]. The ability of the encoded antigen to be presented by MHC class I and class II,

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activating both CD4 and CD8 T cells as well as, indirectly, humoral immunity, is a significant benefit of DNA vaccines [13]. Additionally, because cytosolic sensors can recognize the double-stranded DNA structure in plasmid DNA, the intrinsic components of plasmid DNA can also trigger the innate immune response [13].

2.3. Whole cell vaccine

Whole cell cancer vaccines are a potential method for treating cancer, but it is unclear what makes an immune response work well. Instead of employing single protein or peptide tumor antigens as vaccines, the benefit of using complete tumor cells is that they serve as a source for all potential antigens, negating the need to select the optimal antigen for a given cancer type [14]. Importantly, addressing numerous tumor antigens simultaneously can prevent the issue of tumor antigen loss by inducing an immune response to multiple tumor antigens [14].

2.4. Dendritic cell vaccine

Dendritic cell-based anti-tumor vaccinations have been demonstrated to be a safe kind of treatment during the past few decades. There is a personalized treatment of dendritic cell vaccine named Sipuleucel-T. Prostatic acid phosphatase (PAP; an antigen presents on the majority of prostate cancer cells) and GM-CSF, a fusion protein that promotes the maturation of antigen-presenting cells, were administered to dendritic cells precursors isolated from each patient. The patient is then repeatedly injected with the pulsed dendritic cells throughout numerous cycles. The only vaccine-based immunotherapy and cell-based vaccination currently licensed in the United States for prostate cancer is sipuleucel-T. Dendritic cell vaccines have often received a negative clinical response, but as knowledge grows, more and more complex methods are being researched to boost the effectiveness of dendritic cell-based vaccinations.

3. Challenge and limitation

As a novel therapeutic approach, cancer vaccines encounter several difficulties. The immune suppression issue is the first difficulty. There are several issues with the immune systems of cancer patients because they perform differently from healthy individuals [15]. During the destruction of rapidly proliferating cancer cells, radiation and chemotherapy will target the self-replicating immune cell [15]. The neoplastic cells can also inhibit and kill immune cells in a variety of ways [15]. As a result, cancer patients' immune systems are compromised, which means that standard vaccinations won't be as effective against them.

Another challenge for cancer vaccines is the antigen problem[15]. Unlike infectious pathogens, tumor cells do not express different antigens from normal cells, which means it is hard for the immune system to distinguish tumor cells from normal cells[15]. So, traditional vaccines lower efficacy on neoplastic cells. Only two cancer vaccines have been widely used nowadays. They only can prevent cancer that is caused by viruses: hepatitis B virus, which can induce liver cancer, and human papillomavirus, which can trigger cervical cancer and some other cancer. However, most cancer is not caused by a virus, which limits the efficiency of traditional vaccines.

However, vaccine adjuvant is an excellent approach to solving those problems. There are two classes of adjuvants: immunopotentiator, which helps boost the immune response of the innate immune system by activating different kinds of pattern recognition receptors. Another one is the delivery system, which increases antigen uptake by antigen-presenting cells (APCs) [15]. Vaccine adjuvants play a variety of roles in cancer treatment. The leading roles that adjuvants play in cancer vaccines are listed below [15]:

1. Increasing the function of the antibody.
2. Decreasing the cancer vaccine dose for efficacy immunization.
3. Stabilizing the formulations of vaccines, which are convenient for human use.
4. Improving immunogenicity in the patient.
5. Increasing the number of antigens in blood and duration of response.

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6. Active macrophages and lymphocytes.
7. Enhancing the production of cytokines.

Adjuvants have three ways to improve vaccine efficacy and promote tumor antigen recognition: increasing antigen uptake, cross-presentation, and determinant spreading [15].

3.1. Antigen uptake

During the development of effective antitumor responses, activation of innate immune responses is the most crucial part. Dendritic cells are the first APC to trigger presenting antigen and activate T cells. The approach of tumor immunosuppression includes suppressing DC maturation and activation, as well as the progression of tumor cell companies with the reduced number of activated and maturity DC [15]. Therefore, promoting the APC response plays a vital role in tumor suppression. Cancer vaccines, including an immunostimulatory adjuvant to deliver optimal cancer-specific antigens, can activate APC and prevent unsuccessful T-cell responses [15].

3.2. Antigen cross-presentation

Antigen cross-presentation is essential in presenting immune responses against the tumor after injury vaccination or inducing immune tolerance [16]. DCs can induce an adaptive immune response by activating and migrating toward the draining lymph node [16]. DCs need to process the internalized antigen and load antigen-derived peptides on major histocompatibility complex (MHC) molecules, also called antigen cross-presentation. Therefore, efficient cross-presentation can help induce an adaptive immune response against the tumor. The FDA-approved vaccine adjuvant alum can trigger cross-presentation of tumor-associated antigens [15].

3.3. Determinant spreading

Determinant spreading is a model of autoimmunity in which an autoreactive T cell response, triggered by a single antigenic epitope, evolves into a multi-epitope response[16]. An adjuvant can be used to promote this process in the context of tumor antigens. However, adjuvants also face many challenges. For example, in cancer, adjuvant therapy often uses monoclonal antibodies against CTLA-4, which promote antigen determinant spreading, but it will also cause the acceleration of autoimmune disease in other contexts [15]. Therefore, many problems still need to be solved in vaccine adjuvant treatment.

3.4. Adjuvant combination

Adjuvant combination plays an essential role in cancer therapy. Adjuvant combination vaccines can significantly enhance the immune response by triggering and activating different cell and immune mechanisms [15]. So, the combination is needed to improve the efficacy of cancer therapy since a single adjuvant faces many challenges. For instance, the alum adjuvant vaccine, the only adjuvant cancer vaccine used clinically, is effective in preventing HPV [15]. However, when it mixes with MLP, combining these two adjuvants can stimulate a potent immune response [15]. Also, a new TlR4 against combines with aluminum salts provides similar protection [15].

Although some cancer vaccines affect cancer therapy, most of them still cannot prevent immune-regulatory responses on tumor cells. Also, some vaccines might cause some autoimmune diseases in the patient. Therefore, it is essential to know which kinds of cancer vaccines can increase which immune response. To do so, the multi-adjuvanted are needed. Since a single adjuvant fails to trigger a potent, appropriate, and associated immune response, it is hard to get a clinically relevant antitumor response [15]. However, a combination adjuvant can induce an effective antitumor response and prevent inhibitory pathways [15]. So, more information on muti-adjuvant is needed to overcome the challenges in cancer vaccines.

3.5. Future perspective

Currently, many cancer vaccines still face many challenges, and how to increase the antitumor antigen response is the essential problem needed to solve. Combining several types of adjuvants in the cancer

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vaccine is an effective way to solve current issues. However, more information and technology are needed to increase the efficacy and side effects of the multi-adjuvant vaccine. With the development of combination adjuvant, more effective and personalized cancer therapy will emerge in the next few years.

4. Conclusion

Cancer vaccines gain a great achievement in cancer therapy. Currently, however, only a few types of vaccines are approved by the FDA. Cancer vaccines still face many challenges. The two main challenges are immune suppression and the antigen problem. Although vaccine adjuvant can be a great solution to these problems, more research, and clinical expertise are still needed to improve the efficacy of vaccines.

References

[1] "SEER Cancer Statistics Factsheets: Common Cancer Sites," National Cancer Institute, 2022
[2] S Pallerla, A Ur R M Abdul, J Comeau and S Jois, I*nt. J. Mol. Sci*. **22(2)**, 779 (2021)
[3] J S Ross, E A Slodkowska, W F Symmans, L. Pusztai, P M Ravdin and G. N. Hortobagyi, *The Oncologist* **14(4)**, 320-368 (2009)
[4] U Wiedermann, A B Davis and C C. Zielinski, Breast Cancer Res. *Treat.* **138(1)**, 1-12 (2013)
[5] "Cancer Vaccines: Preventive, Therapeutic, Personalized," Cancer Research Institute, 2022
[6] V Chew, H C Toh and J P Abastado, *J. Oncology* 2012, 608406 (2012).
[7] S-Y Zhu and K D Yu, *Front*. Immunol **13**, 828386 (2022)
[8] L G Salazar, A L Covelera, R E Swensena, T A Gooleyb, V Goodella, K Schiffmana, and M L Disis, *Clin*. Immunol. **125(3)**, 275-280 (2007)
[9] L Zhang, X Zhou, H Sha, L Xie and B Liu, *Front.* Oncol. **12**, 905832 (2022)
[10] C J M. Melief and S H van der Burg, Rev. *Cancer* **8(5),** 351–360 (2008)
[11] M L Disis and J. *Clin*, Oncol. **20(11)**, 2624-2632 (2002)
[12] Z Jahanafrooz, *Drug Discov*. Today **25(3)**, 552-560 (2020)
[13] A Lopes, G. Vandermeulen and V. Preat, J. Exp. Clin. *Cancer Res* **38(1)**, 552-560 (2019)
[14] B P Keenan, E M Jaffee and J. Semin, Oncol **39(3)**, 276-286 (2012)
[15] W S.Bowen, A.K Svrivastava, L Batra, H Barsoumian and H Shirwan, *Expert Rev. Vaccines* **17(3)**, 207-215 (2018)
[16] M Embgenbroich and S Burgdorf, *Front. Immunol.* **9**, 1643 (2018)