Dean&Francis
ISSN 2959-409X

Research Progress and Clinical Prospects of Dendritic Cell Vaccines in Breast Cancer Immunotherapy

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Abstract:

Dendritic cell (DC) vaccines have shown significant research progress and clinical prospects in breast cancer immunotherapy. This article seeks to explain how dendritic cells (DC) show antigens in the immune environment of breast cancer and discuss the difficulties in creating and preparing DC vaccines to make them more effective. The advantages and disadvantages of DC vaccinations and other therapies were evaluated, combined application strategy of DC vaccines with other therapies such chemotherapy, immune checkpoint inhibitors, and radiotherapy was examined. By improving Presentation of an antigen and reducing T cell immunosuppression, the data demonstrated that DC vaccines can have a synergistic effect when used in conjunction with other treatments, greatly boosting the immune system that combats tumors. response. Compared with CAR-T cell therapy, DC vaccines are less likely to cause serious side effects such as cytokine storms. Compared with PD-L1 inhibitors, DC vaccines can actively activate the immune system, produce immune responses against specific tumor antigens, and have immune memory effects. To further enhance the design and administration of DC vaccines and increase their effectiveness in breast cancer immunotherapy, future research should concentrate on the creation of novel vaccine adjuvants, The discovery of new antigens related to tumors and the development of vaccine delivery methods.

Keywords:-Immunotherapy; breast cancer; dendritic cell vaccine; tumor microenvironment; antigen presentation

I. Introduction

Breast cancer is one of the most common malignant tumors in women worldwide. Its incidence continues to rise, especially in developing countries. The prevention and treatment is becoming increasingly severe [1]. Although traditional therapies very important on breast cancer, many patients still face

the challenges of recurrence and metastasis. The rise of immunotherapy has brought forth new treatment options for breast cancer patients, and we need to understand how the tumor immune microenvironment plays a role in its occurrence., development and prognosis of breast cancer has been increasingly valued. A complex ecosystem made up of stromal cells, immune cells, tumor cells, the tumor immune microenvironment works in concert to control the tumor's immunological state and response to treatment [2-4]. Initiating and regulating anti-tumor immune responses is a central role played by DC as key antigen-presenting cells in the immune system [2,5]. Because DC-based vaccinations stimulate The immune system of the patient is capable of selectively recognizing and destroying tumor cells, they are therapeutic potential. DC vaccines have been demonstrated in numerous clinical trials to elicit certain immune responses against breast cancer, which can stop tumor development and increase patient survival [6-8].

This article aims to review the latest research progress of DC vaccines in breast cancer immunotherapy, especially its differentiated application in different breast cancer subtypes and the synergistic mechanism of combined treatment with other therapies. By elaborating on the design principle, antigen loading and maturation stimulation process of DC vaccines, the specific application effects and efficacy evaluation methods in different subtypes. At the same time, the combined application strategy of DC vaccines with chemotherapy, immune checkpoint inhibitors, radiotherapy and other therapies and their synergistic anti-tumor effects are discussed, as well as the comparative advantages and limitations along with additional immunotherapies (like CAR-T cell therapy and PD-L1 inhibitors). At the same time, the challenges faced by DC vaccines in clinical use are analyzed, and their future development direction is prospected, to provide new strategies and ideas for breast cancer immunotherapy.

II. The function of DC within the tumor microenvironment (TME)

DC are the body's most potent antigen-presenting cells (APCs), and they are essential for both triggering and controlling adaptive immune responses. DC are very important in the TME because they can stimulate anti-tumor immune responses by a number of methods in addition to capturing, processing, and presenting tumor-associated antigens (TAAs) to T cells.

A. Antigen Presentation by DC and T Cell Activation

In the TME, DC are able to capture, process, and present TAAs to naive T cells, thereby activating specific anti-tumor T cell responses. This process is mainly achieved through The relationship between the two major histocompatibility complex molecules on the surface of DC and the TCR. In addition, DC also express a variety of co-stimulatory molecules, which bind to the corresponding receptors on the surface of T cells, provide the necessary second signal, and promote the full activation and proliferation of T cells [9]. In particular, DC go through a maturation process after collecting tumor antigens, during which they Migrate to lymph nodes and present antigens to T cells., and increase the production of MHC and co-stimulatory molecules.

B. Immunomodulatory Role of DC in the TME

In the TME, DC have a significant immunomodulatory role in addition to their direct antigen presentation activity. It can influence the function and distribution of other immune cells by secreting a variety of cytokines and chemokines, thereby shaping a microenvironment that is conducive to anti-tumor immune responses. For example, DC can secrete interleukin-12 (IL-12), a cytokine that can enhance the cytotoxic activity of NK cells and CTLs and promote the development of Th1 immune responses [5]. In addition, DC can also guide other immune cells to migrate to the tumor site by expressing chemokine receptors, thereby enhancing the infiltration and anti-tumor activity of local immune cells [5]. In the TME, the function of DC is often suppressed, mainly due to the effects of immunosuppressive factors secreted by tumor cells and immunosuppressive cells [7]. However, through the design and application of DC vaccines, these inhibitory factors can be overcome and the anti-tumor function of DC can be restored [7].

III. Progress of DC vaccines regarding breast cancer subtype classification

The condition known as breast cancer is very diverse. According to molecules classification, it can be divided into multiple subtypes. Different subtypes have different responses to immunotherapy.

A. HER2-positive Breast Cancer

HER2-positive breast cancer is a highly aggressive subtype of breast cancer, and its TME is characterized by specific high expression of HER2 antigen. HER2 protein is expressed at low levels in normal cells, but is overexpressed in approximately 20%-25% of breast cancers, driving the growth and endurance of cancerous cells. Design of DC vaccines for HER2-positive, HER2 protein or its derivative peptides are usually selected as antigens. By loading HER2 antigens onto DC, HER2-specific immune responses can be induced, especially activating CTLs,

ISSN 2959-409X

thereby accurately killing HER2-positive tumor cells. On this basis, the application of DC vaccines further enhances the patient's anti-tumor immune response. A clinical trial incorporated a HER2 peptide-pulsed DC vaccine into the neoadjuvant treatment of early-stage HER2-positive ER-negative breast cancer, showing good feasibility and immunomodulatory effects, and observed the activation of certain T cell reactions [6]. Trial was a non-randomized, open-label study with a total of 31 patients (30 of whom received treatment) divided into three groups (Arm A, B, and C). Efficacy was evaluated by safety data, T cell response indicators, pathological complete response rate, and immunofluorescence analysis [6]. The results showed that vaccine-related side effects included injection site reactions, chills, and fever. In terms of immune response, intra-lymph node injection of HER2-DC1 vaccine induced an increase in T cell response, and intra-tumor combined with intra-lymph node injection significantly enhanced T cell infiltration after chemotherapy, and improved immune infiltration in the TME was observed [6]. This study suggests that the HER2-DC1 vaccine is safe and feasible in neoadjuvant therapy and can improve efficacy by enhancing local immune response. However, the small sample size limits it, lack of formal efficacy testing and direct comparison between groups. It needs to be further expanded to verify its synergy with standard chemotherapy regimens and explore the potential advantages of higher doses of vaccines [6].

B. Cancer of the Triple Negative Breast (TNBC)

TNBC cannot be treated with traditional endocrine therapy or HER2 targeted therapy as a result of the absence of HER2, estrogen receptor (ER), and progesterone receptor (PR) expression [10,11]. More significantly, PD-L1 expression is typically high in the TME of TNBC. One immunological checkpoint molecule is PD-L1. Its expression on immunological and tumor cells can assist tumor cells evade immune surveillance and suppress T cell function. The design of DC vaccines for TNBC requires the selection of other TAAs that are specific or highly expressed in TNBC cells [3]. A study used a retrospective analysis of existing tissue microarray and gene expression data sets to explore the role of CD11c-positive DC in TNBC [11]. The study included tissue microarray samples from 681 TNBC patients who had not received systemic treatment, and integrated two independent gene expression data sets (a total of 244 TNBC cases). It was discovered that the quantity of tumor-infiltrating lymphocytes (TILs), the extent of CD4+/CD8+T cell infiltration, and the development of tertiary lymphoid structures (TLSs) were all substantially favorably connected with the expression level of CD11c [11]. Further analysis revealed that CD11c-positive DC colocalized with TILs and TLSs in the TME, suggesting that they are important on antitumor immune responses. In patients with lymph node metastasis, high CD11c expression was associated with better overall survival [11]. This study suggests that enhancing the number and functional activity of DC in the TME may be a way to improve the clinical outcome of TNBC [11]. However, as a retrospective study, it has the risk of selection bias and cannot establish the causal relationship between CD11c and immune cell infiltration. In addition, CD11c is also expressed in other immune cells, and further analysis of the functional heterogeneity of different DC subsets is needed, and functional experiments should be conducted to verify their specific immune regulation mechanisms [11].

IV. Combining DC with other therapies

The current research focus is on combining DC vaccines with other therapies to enhance the anti-tumor effect through synergistic effects.

A. Combined with Chemotherapy

Chemotherapy is an important component of comprehensive treatment for breast cancer, but its inhibitory effect on the immune system may limit its long-term efficacy. The combined application of DC vaccinations as well as chemotherapy exerts anti-tumor effects through multiple mechanisms, such as enhancing antigen presentation and immune activation, exerting synergistic effects, and regulating the immune microenvironment. For example, chemotherapy drugs induce immunogenic cell death releasing a lot of tumor-associated antigens from tumor cells, which are captured, processed, and presented into T cells [8]. At the same time, DC vaccines can further enhance their immunogenicity by loading tumor-associated antigens released after chemotherapy, strengthening responses on T cells against tumors and encouraging the development of immunological memory, which is crucial for preventing tumor recurrence [2]. This combined application can significantly improve the pathological complete response rate (pCR) of breast cancer patients, demonstrating its effectiveness in practical applications [8].

B. Combined with Inhibitors of Immunological Checkpoint

By reducing T cells' immunosuppressive status, immune checkpoint inhibitors improve anti-tumor immune responses. The combined use of DC vaccines and immune checkpoint inhibitors shows good prospects, for example, the complementary effects of DC vaccines and PD-1 inhibitors. DC vaccines effectively activate and amplify tumor-specific T cells, by presenting TAAs to T cells, thereby initiating anti-tumor immune responses [10]. However,

tumor cells often express PD-L1 to inhibit the activity of T cells and escape immune surveillance. At this time, the addition of PD-1 inhibitors is particularly important. By preventing the activation of the PD-1/PD-L1 signaling pathway, it can reverse the inhibitory effect of PD-L1 on T cells [12]. Specifically, blocking the PD-1/PD-L1 signaling pathway can Encourage the maturation and secretion of IL-12 by DC, thereby enhancing DC-induced T cell proliferation and cytokine (such as IFN-γ) production, significantly amplifying the immune response induced by DC vaccines [12].

C. Combined with Radiotherapy

The combined use of radiotherapy and DC vaccines has shown a unique synergistic mechanism in the course of treating breast cancer. Radiotherapy kills tumor cells through high-energy rays, leading to the cell death process of tumors can involve both apoptosis and necrosis. This process releases a large number of tumor-related proteins. After these proteins are taken up by DC, they undergo processing and appear as antigen peptide-MHC complexes on DC, thereby activating T cells and triggering anti-tumor immune responses. In addition, radiotherapy may also promote the migration and activation of DC by changing the TME, such as regulating the expression of cytokines and chemokines, so that they can more effectively infiltrate tumor tissues and function. The combined use of DC vaccines and radiotherapy has multiple advantages. First, radiotherapy promotes apoptosis and the tumor cells undergo necrosis, increases the availability of antigens, and gives DC vaccines a substantial source of antigens. Second, Radiotherapy-released tumor antigens have the ability to activate DC, which in turn activates T cells, fortifying the immune response in opposition to the tumor. Finally, the combined use of radiotherapy and DC vaccines may produce a synergistic effect. While radiotherapy kills tumor cells, DC vaccines activate the immune system and jointly eliminate residual tumor cells, thereby reducing the risk of recurrence and metastasis. [10]

V. Comparison of the advantages and disadvantages of DC vaccines and other immunotherapies (such as CAR-T, PD-L1 inhibition) in breast cancer

DC vaccines and other immunotherapies each have their own advantages and disadvantages in the management of breast cancer. Choice in therapy requires individualized decision-making taking into account the particular circumstances and characteristics of the patient's tumor.

A. Advantages of DC Vaccines

First, DC vaccines are highly specific. DC vaccines can trigger specific immune responses to specific TAAs, reduce off-target effects, and improve the safety of treatment [7]. Second, DC vaccines have immune memory and can effectively limit tumor recurrence. For example, conventional type 1 dendritic cell (cDC1) vaccines can significantly increase the infiltration of CD4+ Trm and CD8+ memory T cells, thereby improving anti-tumor immune memory [7]. In addition, DC vaccines can provide long-term protection for patients and prevent tumor recurrence through the activation of specific T cell responses and inducing anti-tumor immune memory [2]. Finally, the combined treatment effect of DC vaccines is significantly improved. DC vaccines can be combined with other immunotherapies (like chemotherapy, radiotherapy, and immune checkpoint inhibitors) to generate synergistic effects and greatly enhance efficacy [2].

B. Limitations of DC Vaccines

However, the preparation cost of DC vaccines is high. The preparation process of DC vaccines is complicated, including multiple steps such as DC extraction, culture, antigen loading and maturation stimulation, which leaDC to high preparation costs and limits its promotion in large-scale clinical applications [2,7]. Secondly, there are significant differences in the response of different patients to DC vaccines. Some patients may not be able to produce an effective immune response, which the patient's genetic background could be a factor in the relationship, immune status, and TME [13]. Finally, immunosuppressive factors in the TME may weaken the efficacy of DC vaccines [2]. Therefore, how to overcome the immunosuppressive state in TME is the key to improving the efficacy of DC vaccines.

C. Comparing DC Vaccines, CAR-T, and PD-L1 Inhibitors on Their Effectiveness and Applicability

1) Comparison with CAR-T cell therapy
Genetic engineering is utilized in CAR-T cell therapy to modify specific tumor antigen receptors are expressed by T cells., thereby directly killing tumor cells. This therapy has achieved significant results in hematological tumors, but its application in breast cancer still faces challenges. Compared with CAR-T cell therapy, DC vaccines are safer and less likely to cause serious side effects such as cytokine storms [3,14].
2) Compared with PD-L1 inhibitors
PD-L1 inhibitors enhance Anti-tumor immune responses are a result of relieving immunosuppressive state in T cells. Breast cancer has undergone treatment successful with this therapy, but some patients may not respond well

ISSN 2959-409X

due to immunosuppressive factors in the TME or low PD-L1 expression levels. Compared with PD-L1 inhibitors, DC vaccines can actively activate the immune system, generate immune responses against specific tumor antigens, and have an immune memory effect [3].

VI. Challenges of using vaccines in clinical practice

Although DC vaccines have shown great potential in breast cancer immunotherapy, their clinical application still faces some challenges.

The first is antigen selection and loading. Selecting the right TAAs for loading is the key to DC vaccine design. However, currently, the commonly used TAAs loading methods include HER2, NY-ESO-1, etc. There are differences in the response of different patients to TAAs, and there is still a bottleneck in antigen loading efficiency, which may affect the antigen presentation ability of DC [2,6,15]. Secondly, the maturation state of DC is crucial for their antigen presenting ability. However, immunosuppressive factors in the TME can inhibit the maturation and function of DC, resulting in limited survival of DC in the TME [3]; Commonly used maturation stimulators include TNF-α, IL-1β, IL-6, PGE2, but different stimulators have different effects on DC function, so they need to be optimized according to the specific use of the vaccine [9].

Immunosuppressive factors in the TME may weaken the efficacy of DC vaccines. Therefore, how to overcome the immunosuppressive state in the TME is the key to improving the efficacy of DC vaccines. Currently, researchers are exploring ways to overcome immunosuppressive factors in the TME by combining immune checkpoint inhibitors, chemotherapy or radiotherapy [2,8].

There are significant differences in the immune status of different patients, factors such as the patient's age, genetic background, underlying diseases, and previous treatments may be responsible for this. Therefore, how to create a vaccine treatment plan that is personalized and tailored to the patient's specific circumstances is an important direction to enhance the effectiveness of DC vaccines. Currently, researchers are exploring ways to assess how well the patient's immune system is functioning by testing the patient's immune indicators (such as the proportion of immune cells in peripheral blood, the level of cytokines, etc.), and develop personalized vaccine treatment plans accordingly [2,13].

VII. Discussion

In the treatment of breast cancer, DC vaccines, as a cutting-edge immunotherapy, are gradually showing their profound therapeutic significance and enlightenment. Regarding the therapeutic significance: First, DC vaccines can improve patients' survival rate and quality of life. DC vaccines activate the immune system of the patient, especially T cells, to produce a precise killing influence on the growth of breast cancer cells, which is expected to significantly improve patients' survival rate. For example, DC vaccines for HER2-positive breast cancer patients are capable of triggering HER2-specific T cell responses, thereby improving the percentage of patients who survive without recurrence and who survive overall [6]. Secondly, DC vaccines can promote innovation and advancements in the treatment of breast cancer. Compared with traditional chemotherapy and radiotherapy, DC vaccines have higher specificity and lower toxicity, and can more accurately attack tumor cells while protecting normal cells from damage [10]. This innovative treatment method not only enriches the treatment methods for breast cancer, but also provides a useful reference for the treatment of other malignant tumors. In addition, DC vaccines can boost the effectiveness of combined treatment strategies. The combined use of DC vaccines and other treatment methods (like chemotherapy, immune checkpoint inhibition, CAR-T cell therapy, etc.) can significantly improve the anti-tumor effect. This combination treatment strategy can not only give full play to the advantages of various treatment methods, but also produce synergistic effects, thereby more effectively controlling the growth and spread of tumors. In terms of inspiration: to fully grasp the potential of DC vaccines in treatment for breast cancer, it is necessary to further deepen Acknowledging the function and mechanism of action in DC cells of the immune microenvironment of breast cancer. This includes aspects such as the differentiation, maturation, migration and interaction of DC cells with T cells. By in-depth research on these basic issues, more solid theoretical support can be provided for the design and optimization of DC vaccines. Trial data show that immune-inducing strategies, such as low-dose cyclophosphamide, can enhance patients' sensitivity to PD-1 blockade [5]. Experiments have observed that cDC1 plays a key role in anti-tumor immunity. It can take up and cross-present tumor antigens, thereby activating CTLs and triggering adaptive anti-tumor immune responses [5]. The role of cDC1 in anti-tumor immune responses has been demonstrated by studies, and by enhancing its function or recruiting more cDC1, it is anticipated that the efficacy of cancer immunotherapy will be improved [5].

VIII. Conclusions

As an emerging therapy with a focus on breast cancer immunotherapy, DC vaccines have received widespread attention in recent years. This study, through a comprehensive analysis of existing literature, describes the key antigen presentation function of DC breast cancer's immune microenvironment, summarizes the research progress of DC vaccines that target breast cancer that is HER2-positive and TNBC, analyzes in detail the challenges faced in the process of designing and preparing DC

vaccines, and proposes approaches to enhance the efficacy of vaccines. The synergistic mechanism of DC vaccines and traditional therapies such as chemotherapy, inhibitors of immune checkpoints and radiotherapy, and the the benefits of DC vaccines in the treatment of breast cancer compared with other immunotherapies, are described. Studies have shown that DC vaccines can actively activate the immune responses are a result of the immune system against specific tumor antigens, with high specificity and targeting. DC vaccines also have immune memory effects, which help prevent tumor recurrence and metastasis. Furthermore, when DC vaccines are incorporated with other treatments, they can play a synergistic role, significantly improve the anti-tumor effect, and reduce the side effects of treatment. Finally, compared with CAR-T, DC vaccines are less likely to bring about severe side effects; compared with PD-L1 inhibition, they are less likely to produce drug resistance. However, DC vaccines still have limitations. For example, there are bottlenecks in antigen selection and loading, and different patients have different responses to TAAs. The maturation state of DC is affected by immunosuppressive factors in the TME, and maturation stimulating factors need to be optimized. Immunosuppressive factors in the TME may weaken the efficacy of DC vaccines, and methods need to be explored to overcome these inhibitory states.

Regarding the development direction of DC vaccines, future research can use mRNA technology to design DC vaccines. With the rapid development of mRNA technology, this technology can be used to design DC vaccines in the future to achieve rapid loading of personalized new antigens. Secondly, DC vaccines can be combined with AI and single-cell sequencing technology to screen TAAs with high immunogenicity. This will provide more accurate targets for the personalized design of DC vaccines. For example, the single-cell analysis method mentioned in the study can be further expanded to the screening of TAAs. In addition, to improve the targeting as well as efficacy in DC vaccines in tumor tissues, delivery systems for TME can be developed in the future. For example, intelligent delivery systems can release DC vaccines in a region with high acidity of tumor tissues, thereby increasing the local concentration and efficacy of vaccines in tumor tissues. This will help overcome immunosuppressive factors in the TME and make improvements in the anti-tumor effect of DC vaccines.

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