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Directions for the improvement of dendritic vaccines for HER2-positive breast cancer

Yujie Lin

Chengdu University of Traditional Chinese Medicine, Chengdu, Sichuan, 610075, China

fuliu@ldy.edu.rs

Abstract. Breast cancer is the disease with the largest number of diagnoses at present, which seriously threatens the health of women all over the world. HER2 positive breast cancer is one of the subtypes, accounting for 25% -30% of breast cancer cases. Despite good progress in chemotherapy, radiation therapy, endocrine therapy and other areas, cancer recovery remains a huge challenge. The development of tumor therapeutic vaccines is a promising strategy. In recent years, more and more vaccines based on different carrier platforms have gradually been discovered. These vaccines stimulate the immune system of patients to produce specific immune responses, thereby reducing the recurrence and metastasis rate of cancer. However, in current clinical research evaluations, no type of vaccine has demonstrated significant therapeutic effects. This paper summarizes the mechanism and types of DC vaccine for HER2 positive breast cancer, analyzes its shortcomings according to relevant clinical trials, and proposes solutions in some aspects such as action target, delivery vector, combined immunity, etc, provides a reference for the development and improvement of therapeutic vaccine for breast cancer in the future. At present, many studies are addressing the problems with some vaccines, and there will be better therapeutic vaccines for breast tumors applied in clinical practice in the future, benefiting all humanity.

Keywords: Breast cancer, vaccines, dendritic cells, HER2.

1. Introduction

Breast cancer (BC) has the highest incidence rate worldwide and is the second most common cancer to be diagnosed. It has over two million people infected each year and seriously threatens women's health. In the latest global cancer burden data released by IARC in 2020, there were 870000 cases of colorectal cancer, 770000 cases of lung cancer, 600000 cases of cervical cancer, and 2.26 million cases of breast cancer, which is equivalent to the sum of the previous several cancers, are far more than other types of cancer in women, about twice the total of gynecological tumors, cervical cancer, endometrial cancer, and ovarian cancer [1]. At the molecular level, there are four forms of breast cancer based on distinct receptors; the triple-negative breast cancer (TNBC) and HER2 positive type are the most malignant. At present, chemotherapy, targeted therapy and endocrine therapy are three main clinical treatments for breast cancer. However, for patients with terminal metastatic breast cancer, the above methods are not effective. In recent years therapeutic vaccine for BC has made great progress in phymatology, and its appearance is expected to solve this clinical problem. Tumor vaccine therapy can induce immune

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responses to kill cancer cells through tumor-related specific antigens and reduce the recurrence rate of breast cancer. Nowadays, vaccine development is more targeted at HER2 positive breast cancer with higher prevalence.

HER2 is a member of the receptor tyrosine kinase HER family, which transmits signals through an interconnected network of members. When HER2 related genes are overexpressed or underexpressed, HER2 molecules are more prone to heterodimerization, resulting in the formation of oncogenes. The long-sought discovery of HER2 as an actionable and highly sensitive therapeutic target was a major breakthrough in the treatment of highly aggressive HER2-positive breast cancer [2]. The therapeutic vaccine against HER2 positive BC is mainly based on peptides, whole proteins, cells, viral vectors and genes. Cell-based vaccines are individual specific vaccines developed based on patients' own tumor cells. DC cell is an APC which plays an extremely important role in immunity. It has the strongest ability to extract and process antigens and can present antigens to CD4 or CD8 T cells in the form of MHC.DCs-based CVs were first used to treat malignant melanoma, due to clinical trials and vaccine development technology more mature, DC vaccines are gradually being used as therapeutic vaccines for more tumors. At present, the development of therapeutic vaccines mainly focuses on delivery platforms, preparation technologies, drug dosages, action targets, and so on.

This article focuses on the progress of therapeutic vaccines for breast cancer and mainly introduces the HER2 positive dendritic cell-based vaccine with insights on the improvements of potential targets and preparation techniques and possible future challenges to overcome.

2. Therapeutic vaccines for breast cancer

The advent of vaccines was a significant progress in medical science, which played an important role in preventing and treating diseases. Edward Jenner found the first vaccination in 1796 that cowpox conferred protection to smallpox. Broadly speaking, vaccines are biological agents made from bacteria, viruses, or tumors that can induce specific immunity in the body. Vaccines targeting a specific disease were initially used as preventative measures, with the continuous development of immunology, more and more therapeutic vaccines are being developed. Tumor vaccine therapy activates the immune system through tumor specific antigens, inducing immune responses and reducing the rate of cancer recurrence. With the gradual occurrence of different mutations, the body experiences the emergence of cancer and specific new antigen epitopes, which are ideal targets for cancer vaccines [3].

2.1. Dendritic cells (DCs) -based vaccines targeting HER2 in breast cancer

Most therapeutic vaccines in breast cancer are targeted at HER2. When HER2 is overexpressed, cells can experience abnormal rapid growth due to excessive stimulation, ultimately leading to cancer. Cell-based vaccines in HER2+ breast cancer cover different types such as APC8024, Allogeneic CVS, DCs, Viral vector-based and Gene-based. Dendritic cell vaccines mainly include the following types: tumor antigen peptide-modified DC vaccines, tumor cells and their lysates-modified DC vaccines and gene-modified DC vaccines. Currently, DC cells can be isolated from the PBMC of tumor patients and added TAAs to them in order to obtain the IDCs with TTAs. Then mature DC cells enter the human body, exogenous and endogenous antigens are separately extracted into CD4+T cells and CD8+T cells. Dendritic cells regulate immune tolerance and are involved in initiation of anti-tumour effects, by presenting TAAs to T lymphocytes through the MHC pathway [4]. As they can induce specific humoral immunity, DCs have important roles in controlling immune responses. Dendritic cells-based vaccines can induce specific immune responses in the immune system through antigen presentation to TAA or TSA, thereby killing cancel cells. And the anti-tumor response induced by dendritic cells can exist for a long time, reducing the recurrence rate of cancer.

2.2. Types of DC-based vaccines

2.2.1. Tumor cells and their lysates. It uses lysed tumor cell components to directly impact in vitro to obtain mature DCs. The advantage of this vaccine is that it can provide multiple antigenic epitopes, and

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DC decorated with lysates can stimulate the body to produce more effective immune responses. Many experiments have shown that DC vaccines modified with tumor cell lysates can produce better clinical therapeutic effects. In some animal experiments, tumor cell fragments were used to shock bone marrow cell DC on the mouse breast cancer tumor model to stimulate the body to produce specific immune response. Liu Jianyong et al obtained breast cancer whole cell antigen from the patient himself by repeated freezing and thawing, then activated DC, and then activated TIL by DC. The results showed that the killing rate of T cells to autologous breast cancer cells in vitro was as high as 85% [5].

2.2.2. Tumor antigen gene Encoding tumor antigen genes into DC to stimulate their sustained expression. With the development of molecular biology, sufficient mRNA can be amplified from limited tumor tissues using PCR technology to amplify DC, and differentially screened for specific expression. This method can also induce immune responses against multiple tumor antigens and it can avoid the risk of autoimmune diseases induced by self antigen stimulation of DC [6]. The results of Morse et al 's research indicate the administration of Her-2 expressing DC vaccinations to breast cancer patients at high risk [7]. It can produce an anti-tumor immune response of moderate intensity. The researchers also used Her-2/neu sensitized DC to induce anti Her-2/neu immunity. MUC-1 is a cell surface glycoprotein mainly expressed in epithelial cells such as the breast and ovary. The transcription and translation of MUC-1 gene in tumor cells are significantly enhanced, and it changes its surface sugar chains as specific antigens for immune responses, which are recognized and bound by the immune system. Some experiments transfected the RNA encoding MUC-1 antigen into DC using plasmids and injected into the body through the tail vein of the mouse. These meterial indicate that DC vaccines targeting MUC-1 can induce anti-tumor immune responses.

2.2.3. Tumor cell antigen peptide. Tumor antigen peptide modified DC vaccine is the most studied vaccine in immunotherapy of breast cancer, and it is also the only vaccine put into clinical use at present. After inoculating animals with DC loaded with tumor epitope peptides, it can promote the effective activation of T cells, leading to the regression of tumors with the same epitope peptides. Antigen peptides that can be used for vaccine preparation include tumor antigens, differentiation antigens, tumor idiotypic antibodies, oncogenes and tumor suppressor gene products, mucins, etc [8]. The most significant effect is the MHC restriction peptide, such as CEA, PMSA and HER2/neu. Among them, the therapeutic vaccine against breast cancer with overexpression of HER2 factor has become a research hotspot. Someone before used Her-2 derived E75 peptide to shock sensitize DC. It is used to treat patients with advanced malignant breast cancer, and it can induce specific immune responses in the body without significant adverse reactions.

2.3. The construction of DC vaccines

DCs are APCs that stimulate T lymphocytes to produce immune responses, making them antigen-specific T cells that can kill tumor cells. DC vaccine can irritate the immune response of tumor patients to their own antigens, and it can also target different epitopes at the same time, rather than acting like monoclonal antibodies. The construction of DC vaccines mainly includes two types: in vitro and in vivo. The in vitro method mainly involves loading tumor related proteins or gene modifications after DC induction, and the internal rule is to use antigen and receptor specific binding to target DC. After the vaccine is constructed, it is administered to patients through subcutaneous, intradermal, lymph node, or intravenous injection routes. Preclinical and clinical evidence supports the ability of DCs to induce strong anti-tumour responses against BC cells [9]. For example, in a small clinical trial, the seven patients that have been reported are all in stage II-IV breast cancer, which is brought on by overexpression of HER2. These patients were vaccinated with HER2 intracellular domain (ICD) stimulated autologous DC vaccines after completing post-neoadjuvant therapy with the intention of shielding BC patients with residual illness from relapse. During follow-up, all the 7 patients survived and six patients detected ICD antibodies in their bodies [10]. There are also experiments aimed at exploring the therapeutic effect of DC vaccines targeting HER2/HER3 in combination with

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pembrolizumab, which can improve the effectiveness of the immune-checkpoint inhibitor (ICI). Although Dendritic cells-based vaccines are a promising tumor treatment methods, there are still many unresolved issues. The vaccines have a high demand for production technology and have low clinical benefits, also have a tumor mediated immunosuppressive effect, so it still need to be improved.

2.4. DC and breast cancer cell fusion

One improvement in DC cell-based vaccination methods is to fuse DC with tumor cells. These vaccines must rely on the binding of the vaccine antigen to the host DC, but in many cases, it can lead to immune silencing. However, first fusing DC with tumor cells can express the entire tumor antigen, more effectively stimulating resting T cells and inducing specific CTL. On the other hand, it can express DC related self surface immune factors. There are many experiments to fuse patients' breast cancer cells with their own DC. Afterwards, it can express both tumor related antigen and immune molecules and co-stimulatory molecules derived from DC, thereby inducing specific CTL immune response against autologous tumor cells Polyethylene glycol (PEG) can be used in the fusion of DC-tumor cell hybrids. And PEG can effectively bind two different types of cells together. The efficiency of cell fusion depends on the cell culture conditions. Since cells are sensitive to PEG treatment, this method is most suitable for fusing live cells [11]. In addition, viral fusion membrane glycoproteins can be used to transfect tumor cells and the cells would be precipitated together with DC to obtain DC-tumor hybrid body [12]. DC-tumor vaccines can also be prepared using heat shock and freeze-thaw methods. Although both MHC-I and MHC-II can be better activated by the DC-tumor cell fusion vaccination, it will face greater challenges in production technology.

2.5. Exosome engineering in the infusion pathway

Exosomes are small vesicles that exist in biological fluids and are produced and released by different cells. It has many advantages such as high stability, long communication distance and low immunogenicity. Exosomes contain several types of biological substances including proteins, lipids, enzymes, transcription factors, DNA fragments, mRNAs, miRNAs, and lncRNAs [13]. In recent years, it has gradually become a major contributor to new cancer treatment methods. Exosomes can provide immunomodulators and other types of therapeutic agents to certain targets, as well as deliver different drugs and their genetic information to recipient cells. Therefore, it can be considered as a direction for future vaccine clinical trials.

2.6. Approaches for nano-therapeutic in breast cancer

In recent years, nanoparticles have been a research hotspot, and new approaches to enhancing immunization efficacy in the treatment of BC have been made possible by nanomedicines. Certain nanoplatforms improve anti-tumor immunity's stability and durability by promoting the recognition and presentation of antigen presenting cells, greatly improving adverse side effects. Nanoparticles come in various types such as polymers and lipids, and these NPs have been widely used as adjuvants or carriers to stimulate the immune system. Nanotechnology has raised the detection limit of devices and methods to the molecular level, which enhances the antigen delivery of vaccine carriers to tumor cells. Here, pathogen-specific antigens and nanostructures acting as a vehicle for vaccine components to elicit a regulated immune response are combined to create nanovaccines. They can be developed by simplifying the preparation process, improving technology, and mass production by the company. Nanovaccines can be effortlessly engulfed by APCs, and their antigens and adjuvants can be delivered simultaneously to improve efficiency. Locally administered nanomedicine can remain in TME for a longer period of time, which can enhance immune response. Combining nanomedicine with immunotherapy may make cancer treatment more effective. A large number of experiments have shown that polymer based nanoplatforms are the direction of further research, and how to synthesize novel polymers with low toxicity remains a challenge, leading to the scarcity of polymer based nanovaccines. Moreover, the technical formula and equipment used in this method are much more expensive compared to others. In recent years, there has been great hope for mRNA vaccines in nanocarriers used for immunotherapy, so it is crucial to design

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nanocarriers that protect mRNA from decomposition. Nanovaccines can trigger multiple immune responses, but due to their small size, additional stable components may be added to the vaccine. Since nanovaccines are a novel cancer treatment technique, their toxicity cannot be disregarded in research since their viability and safety have not yet met application criteria.

2.7. DC-based vaccines and immune adjuvants

Adjuvants are substances that enhance antigen immunogenicity and elicit an immune response when inoculated with antigens [14]. Adjuvants are an important component of vaccine development, and most mechanisms are to increase vaccinations' immunogenicity, promote the recognition and presentation of APCs, and stimulate the role of phagocytes. Cancer vaccines containing immune adjuvants can specifically guide and enhance Ag induced immune responses. The use of adjuvants has a history of nearly a hundred years. In addition to aluminum adjuvants, which are widely used in vaccines, many new adjuvants have been developed in recent years, such as Toll like receptor agonists, immune stimulation complexes, nano biological adjuvants, and composite adjuvants. The continuous emergence of various new vaccines has proposed stricter guidelines forward for the development of vaccine adjuvants. However, the use of single adjuvants has decreased as a result of the introduction of new vaccines. The development focus of future vaccine adjuvants will shift towards personalized design and composite effects. However, when selecting different adjuvant strategies for tumor vaccines, there are often differences in targeting tumor antigens, infusion routes, duration of action, drug formulations, and toxicity conflicts. Therefore, it is still necessary to optimize the development and application of adjuvants.

3. Conclusion

Most of the existing methods for treating tumors are based on the immune system. Up to now, methods such as transporting vaccines through nanocarrier platforms, fusing with tumor cells, combining with immune adjuvants, or using ICI have shown significant results. With the in-depth study of HER2 targets, clinical drugs or vaccines based on different epitopes have been developed, providing more possibilities for the cure of HER2 positive breast cancer patients. Vaccines, as an important component of modern immunotherapy, are expected to overcome existing difficulties and benefit cancer patients. This article provides a technical roadmap for future research by summarizing clinical trials and providing examples from literature to illustrate several methods that can improve DC vaccines. DC cells are an important component of specific immune responses. While it may elicit a potent, targeted immunological response by stimulating the immune system, the issues of immune response persistence and cytotoxicity of Dendritic cells-based anti-HER2 vaccines still need to be studied and resolved. In order to enhance the role of DC cells in tumor immunity, in addition to improving carrier loading and combination therapy, further development can also be made in terms of drug delivery pathways and dosage. Therefore, how to apply DC vaccine to clinical trials more effectively and standardize the treatment plan for breast cancer patients is the focus of the next research. Based on past researches on immunotherapy, there will be more innovations in vaccines in the future, bringing good news to human cancer treatment.

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