New therapy against breast cancer: mRNA cancer vaccines

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Abstract: Breast cancer is the common diagnosed cancer around the world with high rate of incidence and mortality. Nowadays, although endocrine therapy, and anti-HER2 targeted therapy got a advance in chemotherapy in the past decades, but our studies face the challenge about the relapse and metastasis of breast cancer. Human beings are in need of innovative treatment strategies to change this situation. Immunotherapy has become the mainstream cancer treatment strategy in recent years. mRNA tumor vaccine has gradually occupied the main position in breast cancer treatment with its special advantages of low toxicity, fast manufacturing and safety, high efficiency, and mRNA vaccine has great advantages over current vaccines. This article mainly reviews the progress of mRNA vaccine in breast cancer, and summarizes the possible challenges.

Keywords: Breast cancer, mRNA, Vaccines.

1. Introduction

In the US, breast cancer is 30% of all newly diagnosed cancers and nearly 0.41 million deaths per year, posing a threat to women's health and well-being [1]. This data is so horrific with constant increasing. Many thesis or data show that there are many potential factors leading to this condition, such as estrogen, family history, gene mutations, aging and so on, which are possible for boosting the development of breast cancer [2]. The breast cancer mainly aims at women who are more possible than men to have this cancer. Although some biological therapies like endocrine therapy, and anti-HER2 targeted therapy get advances nowadays, because of metastatic, breast cancer cells are still difficultly killed totally and can usually infect the other organs that can play important roles like bone, liver, lung [3]. However, the appearance of immunotherapies destroy this confusion.

It is currently believed that the goal of cancer immunotherapy is to activate the anti-tumor immunity of the host, change the microenvironment, inhibit the tumor, and ultimately change the tumor status to improve patient safety. Based on current understanding of the immune system, immunotherapy can be divided into tumor or immune cell vaccines, viral vector vaccines, peptide vaccines, and nucleic acid vaccine [4]. Nucleic acid vaccine is classified into two categories: DNA vaccines and mRNA vaccines. Compared with the other traditional cancer vaccines, mRNA cancer vaccines have more exceptional advantages. There are three points about mRNA-based cancer vaccines. Firstly, compared with virus-based vaccines which are infectious in some situations, mRNA-based vaccines are better [5]. Secondly, mRNA-based vaccines would quickly be translated to protein, when it once enrolls into the cells. Thirdly, the mRNA-based cancer vaccines stimulate immune response to overcome resistance in traditional treatment. Meanwhile, mRNA-based cancer vaccines having no chances to insert chromosome is related with these vaccines have no process of gene mutation. So some Researches have been set up to focus on studying and solving out the instability and the delivery of mRNA [6], there are several types of mRNA-based vaccines'work. The difference between them is the presence or absence of a carrier and the formulation of the wrapped mRNA. The Non-formulated(naked) mRNA-based cancer vaccines are used intradermally or intranodally. Because of instability, non-formulated mRNA-based cancer vaccines would be degraded by extracellular RNases. So nowadays more researches aim at formulated mRNA-based cancer vaccines and get some achievements. This delivery system has three main ways: lipoplex, lipid nanoparticle, Protamine.

mRNA vaccines for cancer currently face several challenges, including immunogenicity, which can trigger an inflammatory response, and difficulty in delivering the antigen accurately to the

predicted site. Additionally, there are production scaling difficulties, mainly in the antigen manufacturing and purification processes, and the cost of vaccine development is very expensive.

In a conclusion, with the development of Immunotherapies, the patients who have cancer have more chance to be treated. Meanwhile, mRNA-based cancer vaccines will be the new trend to treat breast cancer with its special mobility and agency, and the recurrence rate will be down with advantages of avirulence and safety. The potential hazards of vaccine resistance will also be effectively solved out.

This review primarily delved into the development of mRNA-based cancer vaccine, exploring the pathogenic mechanisms underlying breast cancer and gauging the potential future prospects of mRNA-based breast cancer vaccine. Findings from this review suggest that mRNA-based cancer vaccine therapy has become as a highly promising modality for cancer treatment, particularly for breast cancer, with its ability to encode for tumor-specific antigens and activate antigen-presenting cells. Additionally, mRNA-based vaccine platforms offer the ability to simultaneously encode multiple antigens and co-deliver immunomodulatory cytokines, which may potentiate vaccine potency and provide broader immunological coverage. Notably, ongoing preclinical and clinical trials evaluating the safety and efficacy of mRNA-based breast cancer vaccines have discovered promising results, supporting their advancement into late-stage clinical development. However, several challenges remain to be addressed, including issues related to vaccine stability, delivery efficiency, and immunological tolerance. Nonetheless, the field of mRNA-based cancer vaccine therapy represents a significant breakthrough in oncology, holding potential for transforming the landscape of breast cancer treatment in the future.

2. The development of mRNA-based cancer vaccines

The foundation of mRNA vaccines date back to the early 1990s when scientists began to explore the potential of RNA as a therapeutic tool. By direct injection, mRNA transcribed in vitro was totally expressed in mouse skeletal muscle cells, which proved the feasibility of mRNA cancer vaccines. However, because of unstable and its potential to trigger unintended immune reactions, some scientists constantly overcame the challenges by improving the delivery systems of mRNA and modifying the mRNA molecules. What’s more, mRNA vaccines were still in the clinical stage at that time, and the main vaccines used in the fields of cancer to treat patients were inactivated vaccine, virus carrier vaccine. It's worth noting that the mRNA cancer vaccines first got great effect during this coronavirus disease 2019 (COVID-19) pandemic(Both Moderna's vaccine, which uses mRNA technology, and the vaccine developed by BioNTech and Pfizer were about 95 percent effective).There were about 135 million cancer patients worldwide in 2020(Asia accounted for about 48.4% of new cancer patients worldwide).Because of these special backgrounds, the development of mRNA vaccine technology gave entirely new possibilities. From then on, people started to pay more attention to mRNA cancer vaccines. This kind of vaccines with different delivery systems is safer and more stability with the comparison of the other vaccines, which is one of the most significant reasons to become the main vaccines nowadays. Meanwhile, the method of using mRNA vaccines to treat cancer is gradually in the forefront of the world. To date, more than 20 mRNA-based immunotherapies have reached the stage of clinical trials, and have achieved some influential results in the treatment of solid tumors. Although the technology of mRNA-based cancer vaccines are in a immaturate condition, the development of this kind cancer vaccines will be faster with wider range of their effects in the future. According to the newest reports, the well-known American pharmaceutical companies(Modena and Merck)jointly announced that the first mRNA personalized cancer vaccine MRNA-4157 and anti-PD-1 monoclonal antibody (Keytruda) combination therapy entered phase 3 clinical trials ,and most of mRNA-based cancer vaccines were in phase I/II clinical trials at the present.

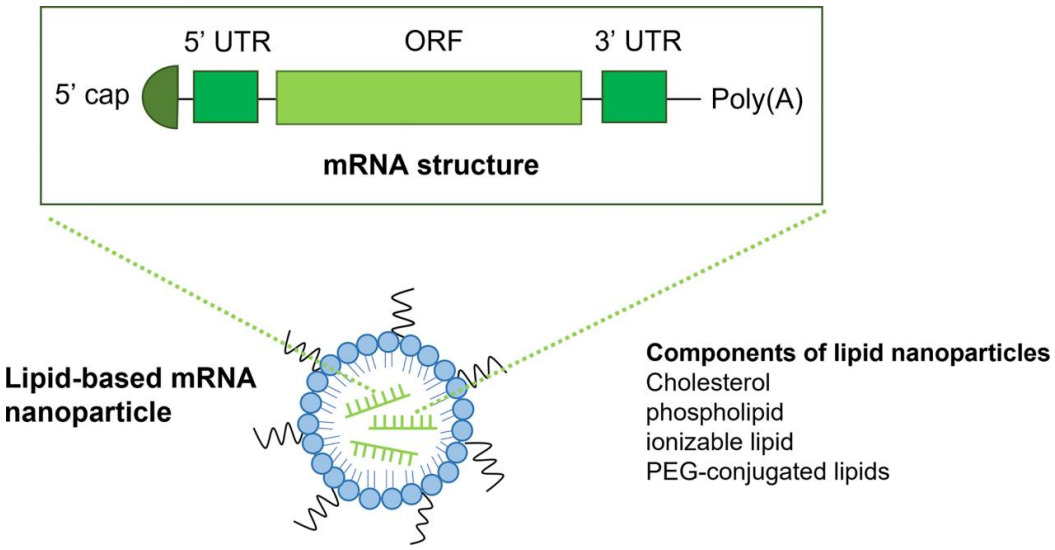


Fig. 1 mRNA vaccine structure [6].

2.1. Mechanism of mRNA-based cancer vaccines

The mRNA consists of 5′cap, UTR, an open reading frame encoding an antigen,3′UTR, and a PolyA tail [7].7-methylguanosine nucleoside which are included by 5 'end cap structure will help prevent the degradation of mRNA from exonuclease. The 5 'and 3' UTR that located on the coding region regulates half-life, mRNA translation, and subcellular localization. Meanwhile, the length of the Poly A tai will influence the translation of protein. A open reading frame encoding an antigen can optimize codons to lengthen the translation of protein.

mRNA vaccines will help bring in a piece of genetic code into our cells. In theory, mRNA would satisfy all needs of genetic information, which causes that these genetic codes will provide the information and orders to cells to produce enough protein. When this kind of protein appear, our body will automatically organize immune response to have some memories about this virus in order to really overcome it next time. This kind of therapy has smaller risks, and it will quickly response to targets with non-toxic environment, which will help overcome the drug-fast of cancer.

The delivery systems are equally important, which in turn, is responsible for the success of development of mRNA-based cancer vaccines.

Compared with the other delivery systems, protamine has been used for the delivery of mRNA vaccines in the early days [8]. Proteins that are positively charged peptides which will connect with negatively charged mRNA to form complexes can prevent the degradation of molecules [9]. Although the achievements in clinical isn't better than that of LNP, polymers have their special advantages that can effectively transmit mRNA. According to the data, Lipid nanoparticles are the most advanced mRNA carriers in clinic, which were used to transmit siRNAs in the past,but with the constant excavating of functions of mRNA vaccines, and now used as the delivery of mRNA .LNPS typically contain four components: ionizable lipids, cholesterol, helper phospholipids, and pegylated lipids, which will cooperatively work to encapsulate and guard against the harmfulness of vulnerable mRNAs.

2.2. Disadvantages and optimizing of mRNA-based cancer vaccines

Although mRNA-based cancer vaccines have achieved many great results, the drawback of these cancer vaccines are still existent. For example, innate immunogenicity are a temporary insurmountable barrier at the present. In theory, these problems will be solved out by Five-prime cap (5'Cap) and Poly (a) tail modification, Optimization of UTRs and open Reading frame and so on.

Of course, based on the better advantages of mRNA-based cancer vaccines with comparison of the other cancer vaccines, the scientists put forward that they need to improve mRNA translation efficiency.

3. Pathogenesis of breast cancer

According to four situations in clinical practice (ER, HER2, PR), the scientists classify breast cancer into three main categories at the present: PR, Er-positive luminal A, TNBC (which is lacking of estrogen receptor), HER2[10]. Meanwhile, from the perspective of pathology, scientists classify the breast cancer into four categories: breast duct cancer, invasive duct cancer, lobular cancer, triple negative breast cancer.

Breast cancer is a metastatic cancer and often metastasize to different organs, which cannot be easily detected by present medical technology and this is the main reason why patients could not be completely treated from ancient times to the present day. Breast tumors usually begin with excessive increasing from the ducts, and during the continuous stimulation of various carcinogenic factors, they develop into benign tumors or even metastatic cancers [11]. This is a slow progress which has six phases(Breast epithelial cell proliferation, Carcinoma in situ, Invasive carcinoma, Cancer tissue spread, Distant metastasis, terminal cancer),usually needs about 10 years and it directly or indirectly kills over 330000 people every year. Tumor microenvironments (macrophages, stroma) which accounts for crucial status in the recognition and prevention of cancer and early eradication is vital in the progress of treating breast cancer. It's noting that Macrophages can produce the inflammatory standard of microenvironment, which can lead to mutation to promote angiogenesis and facilitate cells be able to get rid of immune rejection [12].

In theory, aiming at the development of breast cancer, scientists put forward to two hypotheses: the cancer stem cell theory thinks that all the hypotypes of breast cancer come from the same stem cells or progenitor cells, which causes that different hypotypes of breast cancer are related with these cell that getting mutation and inheritance. The stochastic theory thinks that different hypotypes of breast cancer are from the single stem cells or progenitor cells [13].

There are some gene connecting with the development of breast cancer such as BRCA1/2, HER2, EGFR, c-Myc. The BRCA1/2 are located on chromosome17q21 and 13q12, which are arrestins encoding tumour. Lacking of the BRCA1 will lead to the abnormal duplication of centrosome and instability of inheritance, which in turn, is responsible for the cell apoptosis [14], and the changing of BRCA2 easily causes invasive ductal carcinomas with high grade [15]. Meanwhile, HER2 is more important gene to human beings about breast cancer that is located on chromosome 17 and easily activated by gene amplification and genetic recombination. According to the data, an estimated 20% cases of breast cancer developing by overexpression of HER2. Finally, c-Myc located on chromosome 8 (8q24) will control 15% genes that combining CACGTG or HATs and DNA methyltransferases, and has the essential function in the treatment of breast cancer. Of course, there are the other genes related to breast cancer: H-ras, K-ras and N-ras (are belong to ras family, and located on of chromosome 11,12,1) but not account for the main statues nowadays.

Morbidity of breast cancer depends on some hazards which can not be used to completely explain the pathogenesis of breast cancer now. But as is known to that Genetic factors (family history) are main causes of breast cancer, about 15% of patients have positive familial breast cancer, such as BRCA1、BRCA2、PTEN、ATM、STK11、CHEK2, which influence the morbidity of breast cancer. What' more, there are 100 times more cases in women than men every year.

So human beings should prevent breast cancer in advance. Firstly, aiming at women who are over 40 years old need to have a mammography screening to prevent advanced development of breast cancer because of aging. Meanwhile, according to family risks, people are about 1.7 times than normal people having chances to get breast cancer with a first-degree relative. And this times will be improve to 2.5 when the people have over 2 second-degree relatives. Of course, It is possible that adnormal menstruation and pregnancy will indirectly lead to happen of breast cancer, which needs to be paid more attentions to. And the influence of Estrogen will not be overlooked, which is divided into two types: endogenous and exogenous estrogens. Some researches declare that spay will decrease the risks of getting breast cancer. People also need to refuse excessive drinking, which will improve the level of estrogen in the blood.

4. Future of mRNA-based breast cancer vaccines

Although endocrine therapy, and anti-HER2 targeted therapy get some achievements, but these therapies could not solve out the problems like drug-fast and lacking of pertinence. The therapies of breast cancer consist of endocrine therapy, targeted therapy, Surgery, radiotherapy, chemotherapy. But the curative effect is not ideal. The main reason is that breast cancer gene mutation load is low, belonging to the "immune cold tumor". With the development of vaccines, there are many vaccines developed to treat breast cancer such as Protein-Based Vaccine, Tumor Cell Vaccine, Peptide Vaccine, DNA-Based Vaccine, Carbohydrate Antigen Vaccine, DC-Based Vaccine, DC-Tumor Cell Fusion Vaccine nowadays. Peptide Vaccine is a common vaccine to treat patients with its special advantages of less costs, easy producing, relative stability. But the single peptide is limited to HLA, meaning that patients who can not express this gene will not be treated by this vaccine. What's more, the commen MHC Class I binding peptides are not able to activate CD4+ helper T cells, which may break CD8+ cytotoxic T cells activation and transient immune response. Meanwhile, although the protein-based vaccine will not influence by HLA, the efficiency of this vaccine is extremely low. Tumor cell vaccine aims at using lysis of the whole tumor cells to simulate immune response, but it will cause autoimmune response, which can not contribute to the treatment of breast cancer. And DNA-Based Vaccine has the low efficiency of the expression of plasmids uptake and antigen. And the other vaccines are very difficult to produce in technology, which is connected with the higher costs. With the breakthrough of mRNA cancer vaccines, scientists have chances to turn "immune cold tumor" into "immune hot tumor", which increase the efficiency of treatment of breast cancer under standard of immunotherapy.

First, scientists conducted rigorous selection and research on vaccine targets. The tumor antigens include TAAs, TSAs, TME, TAAs which are the most common target of breast cancer protein vaccines will have priority to be expressed in tumor cells that meet specific criteria. Now scientists use mRNAs to code the TAA in some clinical experiments, and have had some success in melanoma.

Nowadays, the HER2-Positive Breast Cancer are most common. People general use peptide vaccine to treat this kind of breast cancer. But the therapies of situations of TNBC are worse. The immunotherapy of TNBC has the worst prognosis and highest mutation load. And because of no specific antigens, people pay more attention to the choices of target, such as using tumor related antigens like MUC1 and p53 as vaccine antigens for triple negative breast cancer patients. But mRNA vaccines are better and will provide more information and directly insert into the genes with Target gene sequence, because this kind of vaccines can simultaneously express multiple neoantigens that is suitable for the features of tumor specific antigens which are belong to neoantigens and more potential with comparison of normal antigens.

Secondly, in view of the advantages of mRNA, scientists need to conduct further selection and testing of vaccine vectors. Aiming at the breast cancer, the choice of delivery system of mRNA-based breast cancer vaccines are extremely important. As is known to that Non-formulated mRNA-based cancer vaccines are easily changed, so we need formulated mRNA-based cancer vaccines with their special delivery systems such as mRNA-based lipoplex vaccines, Protamine-formulated mRNA-based cancer vaccines, mRNA-based lipid nanoparticle vaccines. Compared with the expensive costs of DCs, the LNPs are more convenience and cheaper and can preform better stability, greater immunogenicity, targeting ability and therapeutic effect in clinical practice for treating breast cancer, which will vastly decrease resistance of industry producing.

Thirdly, the results of the mRNA vaccine for breast cancer are quite remarkable, but from the long-term perspective of the vaccine, the research of this vaccine is still full of great challenges. Although mRNA preform the excellent achievements in clinical practice and have some successful cases in COVID-19, we still need to optimize the delivery systems of mRNA-based cancer vaccines to improve the efficiency of them. For example, the maturation, differentiation and antigen loading of DCs will influence the co-stimulation of T cell, which in turn, is responsible for weak immune response. And the LNPS. Finally, scientists believe that they can successfully turn "immune cold

tumor" into "immune hot tumor" in the future by continuing exploring the fields of mRNA-based cancer vaccines.

5. Advantages and challenges

mRNA vaccine has certain advantages and development potential in breast cancer treatment. This treatment can be introduced into antigen-presenting cells (APCs) via a specific delivery system, synthesizing the desired tumor-specific antigen within the cells, generating a powerful anti-tumor immune response, and having cancer cell toxic activity.

Compared with other solid tumors, breast cancer as a relatively superficial solid tumor, in situ injection method is highly feasible, and can make the selection of antigen targets more extensive. In addition, mRNA vaccines can simultaneously carry multiple tumor-related or tumor neoantigens to stimulate the immune response, thus overcoming the problem of tumor heterogeneity.

However, the application of mRNA vaccines in breast cancer still faces many challenges. The immuno-ecology of tumor microenvironment is closely related to its immunotherapy effect, and the tumor heterogeneity and strong immunosuppressive tumor microenvironment of breast cancer are the main reasons for its unsatisfactory immunotherapy effect. Therefore, further exploration is needed to overcome these barriers, including improved mRNA vaccine design and delivery strategies, as well as in combination with other therapeutic modalities

6. Conclusion

In recent decades, significant advances in mRNA design and nucleic acid delivery technology, as well as the discovery of neoantigen targets, have extremely promoted the application of mRNA vaccines in cancer prevention and treatment. The advantages of mRNA vaccines are reflected in that mRNA cancer vaccines can encode multiple antigens concurrently, as well as the potential for non-integration, high degradation, and no insertion mutations. What's more, breast cancer will be treated by mRNA-based cancer vaccines with the breakthrough of mRNA technology in the future. Although the producing and costs are the main problems of this kind of vaccines, this situation will be quickly solved out by the stronger supports of government and the development of technology.

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