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Vaccine innovations and potential targets of breast cancer

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Abstract. Breast cancer is a concerning worldwide disease that is fatal. Although treatments had been developed over the past, prevention was still on the road of discovery. There are still no vaccines that have been approved for treatment or prevention by the year 2023. In this review, the feasibility of two types of vaccines and potential targets was assessed, with links to future paths of breast cancer vaccine investigations. Messenger RNA (mRNA) vaccine and a tissue-specific self-protein α-Lactalbumin vaccination are two types of potential vaccines facing towards breast cancer with different pathogenesis of overexpression in HER2 or the α-Lactalbumin. Sufficient research had been done on the mRNA vaccines showing HER2 as a potential target that shows the most positive result in vaccine clinical trials. Research on α-Lactalbumin were less compared to mRNA vaccines, but the results showed that α-Lactalbumin was immunogenic enough to induce effective tumor immunity in healthy adult women.

Keywords: mRNA vaccination, α-Lactalbumin, breast cancer, immunoprevention, immunotherapy

1. Introduction

Breast cancer is one of the most common cancers worldwide. According to data from the WHO, 2.3 million women were diagnosed with cancer, and 685,000 fatal cases were reported globally in 2020. Not only females, but males could also be affected by the cancer, with an approximation of 0.5–1% [1]. The cancer was caused by abnormal cell growth inside milk-producing lobules of the breast and ultimately form tumors. When remains untreated until last stage, the tumors may spread in the body and causing risks of death [1]. Treatments includes surgery, radiotherapy, chemotherapy, hormone therapy and targeted therapy. While most of them would work, the adverse effects caused by the treatments were suffering to patients. Ways to prevent the cancer is in necessity. Cancer vaccines are a type of immunotherapy and immunoprevention. Just like other vaccines, they could stimulate the immune system to become familiar with the cancer cell and eliminate it when it appears in the future. Although vaccines were more common for bacteria and viruses, development of cancer vaccines arouse in interest between scientists over the past 50 years [2]. Although peptide vaccine had shown achievements in 5-year survival in phase II clinical trial [3]. By the year of 2023, no vaccines had been proven for clinical usage [4]. Most of the vaccines were still in investigation state. Among the different types of vaccines, mRNA vaccination had shown success in inhibiting breast cancer in pre-clinical and clinical data. In addition, one of the key factors causing unsatisfying results of clinical trials was the insufficient vaccine targets and delivery methods, possible targets of breast cancer vaccine are also considered as a goal for vaccine construction [5]. Vaccination focuses on proteins targeting the mutated BRCA1 genes as a

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prevention of triple-negative breast cancer, which has also shown potential for success in their pre-clinical data. The results of these two types of vaccines show another possible path of research in the future for breast cancer vaccines. In this literature investigation, the feasibility of the mRNA vaccines and the protein-targeting vaccine, e specifically α-Lactalbumin will be assessed and reflected. The major focus of this literature investigation will be sharing the results of human α-Lactalbumin as potential target of the breast cancer vaccination.

2. mRNA Vaccines

mRNA vaccines are becoming a trending vaccination method, mainly due to the success of COVID-19 investments. The first part of this section discusses the results of mRNA vaccines for breast cancer, which have generally shown a good start for further development. The second part of this section will be a comparison of the different types of mRNA vaccines.

2.1. Clinical and pre-clinical mRNA vaccines

mRNA vaccines are known for its ability of delivery massive quantities of patient-specific antigens from a small tumor sample. In addition, RNA vaccines in general could combine with other therapies to achieve a more effective treatment outcome [6]. Compared to the traditional vaccines, mRNA instructs the body to build proteins that enhances immunity against specific microbes [7]. Until 2023, 6 existed mRNA vaccines for breast cancer were in the pre-clinical stage. Because of the characteristics of mRNA vaccines, the target options available have increased compared to the traditional ones. Targeting the selection of the mRNA plays a key role in the ability of the vaccine to enhance the immune response. Among the six, the Self-amplifying mRNA vaccine [8] and Dendritic Cell vaccine [9] targets on the Human Epidermal Growth Factor Receptor 2 (HER2) antigen, while DC also focuses on p53. LNP mRNA vaccine [10] targets on MUC1.

The mentioned vaccines had all shown positive results in inducing T-cell or CTL responses. 9 vaccines were in their clinical stages, SAM vaccine (AVX901) targeting HER2 in had passed phase I with safety and toxicities [11]. No sufficient data is provided yet for its phase II performance as it is still recruiting. Three different DC vaccines targeting CEA, WT1 and Survivin hTERT and p53 had all completed their phase I trials and well-tolerated showing increase in CD8+ T-cell responses [5]. Although none of them had gone through phase II, their results in phase I insinuates a good start. The common target HER2 and had the highest success suggesting HER2 could be the most potential target for further research. T cell activity is the ultimate goal of this type of mRNA vaccination. HER2 is overexpressed in over quarter of the breast cancer cases, causing increase in metastasis and poor prognosis. The Viral-based HER2 RNA vaccines have shown success in stimulating potent HER2-specific T cells particularly the memory CD8+ T-cells with increased PFS [8].

2.2. Types of mRNA

Two major types of mRNA are selected for breast cancer vaccination: self-amplifying RNA, which has already gone through clinical phase I, and conventional non-replicating mRNA, which is classical eukaryotic mRNA. Both of the mRNAs contain a poly-A tail and 5' cap with untranslatable regions. The conventional non-replicating mRNA had an open reading frame in between the UTR which is used and requires further modification to improve the anti-tumor immunogenicity of the vaccine. This type of vaccines is modified to imitate a fully processed mature mRNA molecule in a eukaryotic cell with the same structure described above. The difference between the vaccine and the actual RNAs were the coding and modification on deletion of unwanted responses and enhancing the translation efficiency [6].

The structure of alphavirus-derived SAM consists of two ORFs and a sub genomic structure between the frames. The two ORFs in a single strand encode with a replicate complex and gene of interest for vaccine driven by single-stranded RNA virus-derived subgenomic promoters. These types of vaccines are also known as the replicon vaccines based on the structural characteristics of the ssRNA viruses excluding the viral components. Unlike conventional mRNA vaccines, SAM vaccines advantages in their ability of lowering doses in 5-200 times efficiency due to the applied expression systems [12].They

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are also more flexible to use in immunization studies, suggesting this type of mRNA could be a rising star in the future investigations.

3. Human α-Lactalbumin Targets

In this approach, the vaccination was developed against a self-protein that were not used anymore from the expression at immunogenic levels over aging. In breast cancer, these types of proteins were overexpressed in the tumors. The α-Lactalbumin is a type of those self-protein by its high frequency of expression normally in late pregnancy and lactation but shown the same level in triple negative breast cancers which is the most aggressive and fatal form of breast cancer. Women with mutated BRCA1 genes are at the high risk of the α-Lactalbumin overexpression [13].

3.1. α-Lactalbumin vaccination preclinical data

In a report from 2016 [13], the α-Lactalbumin vaccination was tested on healthy, cancer-free adult women. To find out whether immunologically response will appear in adult woman, lactation will cause tolerance difference, the efficiency of the vaccine to the tumor and if non-breast tissues would also be affected. The experimental data was provided in success in T cell responses both in vitro and in vivo. Database searches were also done by the research group to reassure the overexpression of α-Lactalbumin in cases of triple negative breast cancer. The methodology this research group used was RT-PCR, Western blot and immunohistochemical analysis on human tissues with in vivo growth of the tissues in immunodeficient mice. Finally, the gene expression was measured for its bioluminescence from growing human HCC1937 TNBC cells.

3.2. Methodology and results

One limitation of this research was that the feasibility of their vaccine will be easily affected by the T cell repertoire capability of mounting proinflammatory immune responses to α-Lactalbumin and this is an uncontrollable variable that each sample patients will have difference in their individual abilities naturally. The research group tries to eliminate the influence by evaluating the size of the T cell repertoire induce by priming of PBMC to α-Lactalbumin. Then, the T cells were tested for recalling responsiveness in ELISPOT assays. As a result, the sampling healthy women have T cell response with a frequency similar to the samples they obtained in vivo in mice vaccinated against α-Lactalbumin. Those adult women were likely to have the T cell repertoires capable for performing the response sufficient to induce effective tumor immunity [13].

The result in lactation and breastfeeding history further excludes possibilities and factors influencing the efficiency of the vaccine for further adjustments. The induction of effective tumor immunity against the target protein will be affected by the tolerant states. The research group conducted a compared study of the T cell immunity and tumor protection by mice with and without the influencing factor by mating the mice and complete a full cycle of pregnancy, lactation, breastfeeding and weaning to model real life human situations. Then they wait for four weeks and immunized them. After another four weeks, the result shows that the history of lactation and breastfeeding would not impact on the frequencies of proinflammatory T cells, or the effectiveness of tumor immunity induced by the vaccination [13].

PCR of genes had done with the supported database research [14, 15] to test the efficacy of the vaccination to the breast tumor. RNA was extracted from human TNBC ells and reverse transcribed and amplified for human α-Lactalbumin and β-actin. Agarose gel electrophoresis was then used to amplify the products. The RT-PCR amplification and Western blot analyses shows the gene expression of α-Lactalbumin, and protein detected in human TNBC cell lines had varied in degrees [13].

The same methods were applied again to the TNBC tissue blocks to assess the a-Lactalbumin gene expression in tumor tissues for later comparison. By using α-Lactalbumin-specific antibody, the TNBC tissue sections showed 83% varying degrees of cytoplasmic immunoreactivity under immunohistochemical analysis [13].

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3.3. Conclusion of α-Lactalbumin vaccination

From the report, it is fair to conclude that adult women have the availability for proinflammatory T cell repertoire respond to α-Lactalbumin. α-Lactalbumin is sufficiently immunogenic to induce effective tumor immunity in women. Suggesting α-Lactalbumin could be the next target for breast cancer vaccine developments. Similarly, to the mRNA vaccines, the α-Lactalbumin vaccines could occur in combination with another adaptive proinflammatory T cell response. Although the results are inspiring, further research and trials should be done to reassure the results. The mechanism of α-Lactalbumin overexpression in TNBC still remains mysterious. A hypothesis is the loss of default inhibition influenced by the level of estrogen and progesterone could be a reason. In addition to the results, the research addressed that the TNBC tumors were found to grow in complete absence of cognate signaling of estrogen and progesterone [13].

4. Conclusion

In conclusion, mRNA vaccines have shown a great start in breast cancer development that 9 of them are in clinical stage I. The HER2 overexpression is one of the modest targets that future research could focus on since it links with the memory CD8+ T-cells responses. Among the different types of mRNA, self-amplifying RNA is the most effective genre that could be more efficient and saves doses compared to the conventional RNAs, suggesting that the SAM vaccines could be the spotlight in future breast cancer vaccine research. In addition, the SAM vaccine is the one that has made the furthest progress in clinical trials, having successfully passed safety and toxicity checks in Phase I and moved on to Phase II. The α-Lactalbumin is a self-protein that links with breast tumors. The vaccine targeting α-Lactalbumin and proinflammatory T cell repertoire response could be the goal of research targeting triple-negative breast cancer patients with α-Lactalbumin overexpression. While the mechanism remains unsure, research could also be done to analyze the reason of the irregular expression. The research done by Tuohy et al. provides firm evidence of the feasibility of the pathway for investigating proteins as a target for breast cancer vaccines. Combination therapy could be used in both mRNA vaccine and vaccines targeting α-Lactalbumin. Ultimately, both vaccines were designed to insinuate T cell response to inhibit the tumor.

As a reflection on this research, the amount of evidence for assessing α-Lactalbumin as a potential target was not sufficient compared to that of the mRNA vaccines, where only one set of data and an example were used. More documents and data should be included to support the research findings by the research group. The mechanism of mRNA vaccines could also be explored further. Tumor cells' resistance to immunotherapy is a potential topic of research for further investigation inspired from the vaccines' research.

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