Vaccination Therapy: An active approach towards Triple-Negative Breast Cancer

Caizi Niu[1, †], Jiaying Shi[2, †, *], Hanfu Zhang[3, †]

[1]School of Westa, Southwest University, Chongqing, China

[2]School of medical science, University of Sydney, Australia

[3]School of molecular science, University of Western Australia, Australia

*Corresponding author: jshi4672@uni.sydney.edu.au

† These authors contributed equally

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Abstract: Breast cancer is presently one of the most prevalent malignancies in females. Among all types of breast cancer, triple-negative breast cancer (TNBC) is considered the most challenging subtype to treat due to the absence of chemotherapeutic targets such as ER, PGR, and HER-2, the ease of recurrence, and the high rate of metastasis. Based on its sensitivity to chemotherapy, chemotherapy and neoadjuvant therapy for TNBC was developed and so achieved breakthroughs recently in the treatment of TNBC. Nonetheless, the prognosis for chemotherapy in partial responders and recurrent patients is often poor, and there is no conventional treatment protocol. In these years, the Vaccine-Based Immunotherapy Regimen has emerged as a promising immunotherapeutic option with the advantage of relapse prevention as well as safety and patient specificity, and the autologous tumor cell-based vaccine can benefit from training the patient's immune system to recognize and eliminate the occult disease. To discuss the possible therapeutic applications that will be evaluated and predicted future directions, this paper reviewed three vaccine targets utilized in TNBC in recent years, Folate receptor alpha (Frα), Mucin 1 (MUC1), and Cancer Testis Antigen (CTA). From the standpoint of vaccination therapy, their principles, effects, and results of relevant clinical trials phases for TNBC are also discussed, and make our suggestions for further development.

1. Introduction

Triple-negative breast cancer (TNBC) is a special type of breast cancer that is negative for estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor (HER2). With the lack of these specific targets expressed, traditional targeting therapy, which is usually induced by hormone, Tinib drugs, and monoclonal antibodies could be invalid, making chemotherapy became the most effective treatment under the current situation. However, chemotherapy has limited efficacy and seriously affects the quality of life, making a general agreement is that more attention should be paid to other more promising targeted therapies [1].

A vaccine, a kind of biological preparation that carries specific substances, is usually a product that achieves the purpose of disease prevention and control by stimulating the immune system to produce an immune response against the characteristic antigen [2]. Such antigen can be either exogenous, such as a specific section from bacteria/virus that caused infectious diseases; or endogenous, such as some special sections on the surface of tumor cells. Unlike monoclonal antibodies or adoptive immunotherapy, vaccine therapy more focuses on using and training the patient's immune system to produce antibodies against cancer cells. Therefore, vaccine therapy is considered a special kind of immunotherapy and is called "active immunotherapy" [3]. In the case of immunogenicity with a normally functioning patient's immune system, the characteristic of rapid, low-cost, strong endurance, anti-metastases, and prevention of recurrence of vaccine therapy will greatly improve the prognosis of patients [3].

Due to the absence of target receptors such as ER, PGR, and HER-2 in TNBC cancer cells, the patients cannot profit from hormonal or trastuzumab treatment and are usually treated by chemotherapy [4]. As a systemic option, The common chemotherapy regimens involved in P53 analogs (e.g., taxanes), targeted DNA repair complex analogs (e.g., platinum compounds and paclitaxel analogs), cell proliferation analogs (e.ganthracycline-containing regimens), and targeted therapies [5]. Neoadjuvant therapy has followed suit with recent breakthroughs in the treatment of TNBC [6]. On the one hand, the prognosis of chemotherapy in incomplete responders and relapsed patients is usually poor without a standard treatment regimen. TNBC is often aggressive and drug-resistant when metastases occur, leading to extremely high mortality [7]. On the other hand, the Vaccine-Based Immunotherapy Regimen has emerged as a promising immunotherapeutic option with its advantage of relapse prevention, and the autologous tumor cell-based vaccine can benefit from training the patient's immune system to recognize and eliminate the occult disease with its advantages of safety and patient specificity.

2. General principles and forms of Vaccine therapy in TNBC

Currently, a variety of treatments for triple-negative breast cancer are being developed. For a better utilizing of vaccine therapy, it is significant to understand its unique basic principles and fundamental advantages. Defined as "active immunotherapy", vaccine therapy is quite different from other immunotherapies, which are closely integrated into the treatment process after diagnosis and treatment. Vaccine therapy can stimulate the immune system, which intensifies the CD4+ helper T lymphocytes and CD8+ cytolytic T lymphocytes responses or prevents the immune response suppressors [7]. At the same time, as vaccine preparations trigger a large-scale immune response through a small number of substances, vaccine therapy may also produce immunotoxicity with improper antigens. Therefore, it is necessary to have a unique evaluation and supervision mechanism, along with an advanced clinical evaluation test system to ensure its low-cost, high efficiency, and safety during the treatment [8].

Cancer vaccines that are currently entering clinical trials and treatments have possessed the above characteristics [9]. However, in addition to these basic requirements, researches on vaccine therapy should also focus on indicators such as response rate (OR) and overall survival (OS). Over the years, numerous research groups have used a variety of approaches to therapeutic vaccination. Considering the different delivery methods and strategies of these methods, which may differ in vaccine efficacy. [10]

In addition to the delivery method and presentation form of the antigen, the choice of the type of antigen itself is another part that needs to be considered during the procedure of designation and production of the vaccine. Theoretically, the choice of delivery and antigen source have to guarantee the effectiveness, immunocharacteristic with as little side effect as possible [11]. Razazan and Behravan et al. concluded in 2019 that there are seven vaccine classifications in the single peptide and combination classification of triple-negative breast cancer. Among them, the more promising antigen types in recent years are folate receptor alpha (Frα), Cancer Testis Antigen (CTA), Mucin 1 (MUC1), etc. [11]. Therefore, in the following part, we will focus on introducing and discussing vaccine therapy based on these three types of antigen.

3. Human Folate Receptors

3.1 The prospect of targeting folate receptors as a treatment for cancer

Water-soluble Vitamin B9 (folic acid and folate) is associated with single-carbon metabolism, DNA biosynthesis, methylation, and repair in rapidly proliferating cells [12]. The human folate receptors (FRs) are high-affinity receptors that are mediating transportation of tetrahydrofolate via endocytosis, which is essential for maintaining bodily functions, and with four glycopolypeptide receptor members: FRβ, FRα, FRδ and FRγ (molecular weights ranging from 38~45 kDa). FRγ is freely soluble due to the lack of glycosylphosphatidylinositol (GPI) components, which is found only in hematopoietic

cells, whereas the α isomer is anchored by GPI to the cell membranes of mammary ducts, lung, kidney, choroidal plexus, and as well β isomer is attached on activated myeloid cells via GPI [13].

The characteristics of FRs are over-expression on multiple tumors that allows them to be used as biomarkers (e.g., non-small cell lung cancer) and tools of diagnosis and therapy for specific targeting and imaging of cancer cells [13]. It has been proposed that depending on the over-expression of FRβ in Tumor-associated macrophages (TAMs), folate-modified lipoplex comprising a folate-modified liposome (F-PLP) was utilized as a novel gene vector to target FRβ in the tumor microenvironment and lung cancer cells, thereby inducing apoptosis and reducing tumor proliferation [14]. Decades after the development of drugs targeting intracellular folate metabolisms such as methotrexate and pemetrexed, the high expression of FRα has enabled it as a recognized anticancer target [15] and the potentially targetable solid tumors including TNBC [16], ovarian cancer, and lung cancer [17].

3.2 The feasibility of FRα as a potential target for the treatment of TNBC

Combined with the fact that TNBC accounts for up to 15-20% of all invasive breast cancers, its poor prognosis [16], as well as a mortality rate of approximately 40% within five years of diagnosis and high invasiveness it is urgent to find a standardized treatment protocol for TNBC [1].Previous research carried out immunohistochemistry on paraffin sections utilizing a polyclonal FRα antibody indicated that FRα is highly expressed in up to 85% of TNBC while having limited expression in healthy tissue [18]. Similarly, another related study confirmed the expression of FRα in 384 TNBC patients by immunohistochemistry assay and showed that FRα expression was detected in nearly 71% of cancer lesions (274) and was associated with invasive disease-free survival (IDFS) [16]. Besides, high histologic grade and advanced stage were also correlated with FRα expression [18]. Therefore, it is a potential biomarker and therapeutic target for TNBC due to its better prognosis, high expression, and high selectivity.

3.3 Therapeutic vaccine for TNBC

TPIV 200 is based on the FRα vaccine for TNBC developed by immuno-oncology TapImmune, Inc. The clinical trials of the vaccine are currently in Phase II, and the Data Safety Monitoring Board (DSMB) has given an upbeat assessment of the current progress that can continue to be administered routinely to TNBC patients [19]. TPIV 200 is an innovative vaccine containing five immunogenic peptide antigenic epitopes originated from FRα that effectively stimulate antineoplastic activities and immunomodulation in primarily anti-TNBC and platinum-chemotherapy-resistant ovarian cancer in clinical trials [20]. TPIV 200 works by inducing cytotoxic T-lymphocytes and CD4+ cells to mount an immunological response against high FRα levels of tumor cells [21].

A phase I clinical trial (NCT01606241) evaluated the side effects of therapy with one cycle of oral cyclophosphamide followed by six months of intradermal vaccination (TPIV 200) in 24 participants with ovarian and triple-negative breast cancer and the safety with ability to elicit a robust immune response [22]. The results showed that 91% of patients developed a strong and at least 12-month-sustained immune response (activation of FRα specific T lymphocytes or high-affinity antibodies), which was effective in killing cancer cells [23]. Meanwhile, a randomized multi-center phase II trial (NCT02593227) evaluate the safety and immunogenicity of two doses of FRα peptides (TPIV200) as well as a GM-CSF combination vaccine (with or without cyclophosphamide immune primers) in patients with primary TNBC [24]. The combination regimen can be used to consolidate treatment in patients with stage IIb-III TNBC after neoadjuvant or adjuvant therapy, whose primary endpoint was to detect the ubiquity of an immune response (B and T cell immunity); secondary indicators were safety and tolerability, relapse-free survival, and FRα expression [24].In addition, there is an ongoing Phase II clinical test treatment of TPIV200/huFR-1 mixed with GM-CSF plus Anti-PD-L1 MEDI4736 (Durvalumab) test the safety and efficacy of the two investigational agents (NCT02764333), which will be assessed as consolidation therapy (after platinum-based chemotherapy for ovarian cancer patients) [25]. Notably, TPIV200 is designated by the US Food and Drug Administration (FDA) as an orphan drug (a treatment modality for rare diseases) given for the treatment of ovarian cancer [26].

A phase II, parallel-group, double-blind, controlled, randomized protocol clinical trial (NCT03012100) investigated the efficacy of a multi-epitope FRα vaccine, sargramostim (GM-CSF) and cyclophosphamide as a combination treatment regimen in preventing recurrence of stage I - III TNBC [27]. The vaccine, made from a mixture of leukocytes and tumor proteins, stimulates an effective immune response to kill tumor cells as well as a complementary therapeutic agent to inhibit the growth and division of cancer cells to prevent their invasion [28].

Two clinical trials of FRα-based TNBC vaccines were completed at I/II phase (NCT01606241, NCT02593227), respective resulting were shown that 16 of 16 patients with observation data had demonstrable T cell responses persisting into the observation phase, and No descriptive result published yet.

4. Prospects for the target of MUC1

Mucin 1 (MUC1) is mucin that functions as a transmembrane glycoprotein. Abnormal expression of MUC1 has been found in a variety of tumor cells, among them, which is most prominent in breast cancer cells. In human cancers, abnormal glycosylated MUC1 is associated with the transformation of normal cells into cancer cells. Therefore, tumor vaccines based on MUC1 are promising for preventing breast cancer development and metastasis [29].

4.1 Role of MUC1 targets in humans

The regulation of the expression of MUC1 and its expression location may be involved in the regulation of anti-adhesion [30]. MUC1 is expressed in epithelial cells of various tissues and organs, which functions primarily in the formation of a physical barrier to lubricate and protect normal epithelial tissues and mediate signal transduction [31]. MUC1 can down-regulate the expression of E-cadherin, which is one of the steps to enhance the invasiveness of tumor cells. It has also been reported that the high-density expression of filamentous MUC1 molecule on the membrane surface of cancer cells can block the interaction between the fixed ligand and its receptor on the membrane surface, and reduce the integrin-mediated intercellular interaction in the extracellular matrix [32]. Meanwhile, the Sialy-Lewisx epitope on MUC1 can act as the ligand of E-selectin and interact with E-selectin on injured or inflammatory vascular endothelial cells, so that tumor cells can easily adhere to vascular endothelial cells and pass through the vascular wall, and thus facilitating the metastasis of tumor cells.

4.2 Association of MUC1 with TNBC

Current studies have shown that MUC1 can induce anti-maneoma CTL immune response (MHC-restricted and non-MHC-restricted), and inhibit the killing effect of immunoactive cells against tumors. A high expression level of MUC1 is negatively correlated with the prognosis of tumor patients, suggesting that MUC1 may be involved in the regulation of immune response.

Finn et al. firstly discovered the presence of cancer-killing CTLS in patients with breast, ovarian and pancreatic cancer, characterized by non-MHC restriction. Subsequently, CTLS with MHC I restriction recognition of MUC1 epitopes was identified in breast cancer patients [45]. These phenomena were further confirmed in mice, suggesting MUC1 can be a molecular target of cancer biotherapy.

When cells became cancerous, MUC1 functioned in tumor cell proliferation, epithelial-mesenchymal transformation, immune escape, and tumor cell epigenetic remodeling. Aberrantly glycosylated MUC1 is a recognized tumor-specific antigen on epithelial cell tumors [33]. Compared with normal MUC1, aberrant MUC1 has different characteristics, which affect cancer progression, including (1) expression levels increase several times; (2) changes in cell surface distribution, loss of polarity distribution, expression of the entire cell surface; (3) structural changes, mainly due to incomplete glycosylation [34], new glycochain and peptide epitopes appeared [35].

4.3 The MUC1 target interacts with other factors

MUC1 can interact with many factors. As cell surface receptors, they interact with various protein kinases after phosphorylation at tyrosine sites in cells and participate in signal transduction pathways. Fibroblast growth factor receptor (FGFR) and platelet-derived growth factor receptor (PDGFR) are essential receptors for tyrosine kinases [36]. Previous research has shown that PDGFR interacts with MUC1 to promote tumor growth, invasion, and metastasis [37]. In addition, MUC1 is a substrate and effective regulator of erbB1. When MUC1 was combined with erbB1, stability of erbB1 receptor was activated and transformation may be promoted by inhibiting erbB1 degradation [38]. In breast cancer cells, phosphorylation occurs in the cytoplasmic domain of MUC1-C mediated by epidermal growth factor receptor (EGFR). This result was shown to be associated with decreased activity of pyruvate kinase M2 (PKM2) [39]. In addition, the interaction between MUC1 and NF-κB (Nuclear factor-Kappa B) induces the expression of INTERleukin-6 (IL-6) and tumor necrosis factor-α(TNF-α), forming a pro-inflammatory tumor microenvironment [40].

4.4 Clinical manifestations of vaccines targeting MUC1

Nowadays, a research team designed a variety of tumor vaccines with MUC1 as the target antigen and conducted phase I-III clinical trials. In this part, we reviewed the research history of the tecemotide vaccine from Merck in Germany in the field of lung cancer and discussed the development direction of tumor vaccines. Tecemotide (L-BLP25) is a long peptide liposome vaccine specific to MUC1 antigen. Preclinical and phase I studies suggested that tecemotide effectively activated MUC1 antigen-specific T cells, inhibited the growth of lung cancer in MUC1 transgenic mice, and significantly prolonged the survival of lung cancer patients who responded to the vaccine In a Phase IIB trial involving 171 patients with stage IIIB/IV non-small-cell lung cancer (NSCLC). Moreover, 3-year overall survival was significantly higher in the tecemotide group than in the control group (31% vs. 17%, P =0.035), with a median increase in survival of 4.2 months, but there was no statistically significant difference. On this basis, the randomized, double-blind, global, multicenter Phase III clinical trial (START) enrolled 1513 unresectable stage III NSCLC patients who achieved stable or clinical response with chemotherapy to evaluate tecemotide as a maintenance therapy strategy. Median overall survival was 25.6 months for tecemotide and 22.3 months for placebo, with no significant survival benefit in the vaccine group. In subgroup analysis, tecemotide extended median survival by 10.2 months compared with placebo in patients who had previously received concurrent chemotherapy, showing a significant survival advantage (P =0.016). In 2014, Merck launched a Phase III clinical trial called START2 to explore the efficacy of tecemotide in lung cancer patients who had been effectively treated with concurrent chemotherapy. It is a pity that the Phase III similar clinical study (NSPIRE) in Asia failed again, and the START2 study was suspended after one of the subjects experienced serious side effects [41].

Through analysis, we concluded that the efficacy of therapeutic vaccines should consider the following factors, (1) Antigen selection; (2) Effective presentation of antigen; (3) Individual differences; (4) Tumor immune microenvironment. MUC1 also exists in normal cells but is highly expressed in tumor cells. The body's immune system will develop immune tolerance to these "self" proteins, and will not produce a strong immune response, leading to the failure of the tumor vaccine.

5. Cancer Testis Antigen (CTA): A new strategy.

Cancer Testis Antigen (CTA) is a general term for a class of antigens. There are more than 100 known cancer-testis antigens (CTA), many of which are important TAAs [42]. As a testicular antigen, CTA is important for testes that cannot initiate an immune response and lack the adaptive immunity and blood testicular barrier that can isolate germ cells, because they provide an immune-privileged microenvironment to complete the meiotic process [43]. Recent studies have found that CTA is not expressed in normal tissue cells, but its expression has been observed in malignant tumors with various cancer types, including TNBC [43]. In many reported cases of TNBC, the expression of different members of CTA has been reported as well, among which NY-ESO-1 and MAGEs (A1-A4) are the

most abundant in other CTAs. Some experiments have even shown that compared with ER-positive tumors, MAGE-A and NY-ESO-1 have significantly higher expression levels in TNBC [44]. In investigating 8 CT antigens, further studies showed that MAGE-A, CT7, NY-ESO-1, CT10, CT45, GAGE, SAGE1, and NXF2, among all 454 BC patients, were showing significantly high expressions in 225 TNBC cases [43]. This characteristic of tumor cell-specific and generally high expression makes these TAAs suitable candidates for TNBC vaccine targets [11].

5.1 Case study indicates how a typical novel NY-ESO-1 targeting vaccine work

Currently, among all CTA targets, NY-ESO-1 is considered to be one of the most mature vaccine targets. As the first clinical trial of the NY-ESO-1 targeting vaccine was conducted more than ten years ago, we already have a system consisting of single synthetic peptides, single and complex recombinant proteins, and various adjuvant formulations. Injecting the antigenic peptide along with adjuvants is an effective strategy, which enhances the activity of cytotoxic $CD8^+$ T lymphocytes when exposed to MHC class I restricted peptides. Among the antigenic peptides, NY-ESO-1 can significantly increase humoral and cellular responses targeting the tumor [45]. An alternative strategy of enhancing the effectiveness is to induce a $CD4^+$ immune response to support the activation and maintenance of $CD8^+$ cytotoxic T lymphocytes [46]. Currently, the NY-ESO-180-109 and NY-ESO-1157-165 peptides, which are associated with $CD4^+$ and $CD8^+$ T cell responses respectively, have been proved to be the most immunogenic so far [46]. In addition, using long peptides may also induce a strong immune response. For example, inoculation of 20-mer NY-ESO-191-110 peptide, covering multiple epitopes, induces $CD4^+$ and $CD8^+$ T cell responses in body fluids and cells [48].

Recently, Patel et al. designed a NY-ESO-1 vaccine based on biomimetic nanomaterial platform technology. The vaccine uses a 30 nm diameter icosahedral plant virus cowpea mosaic virus (CPMV) to carry multiple copies of the human HLA-A2 restricted peptide antigen NY-ESO-1157-165 [47]. Due to its unique, highly ordered 3D architecture, CPMV has become an ideal platform of epitope displayment that in addition to carrying antigens, the virus protein scaffold allows the activation of pathogen-associated molecular pattern (PAMP), the pathway to induce specific immunity, and the viral nucleocapsid binds to several pattern recognition receptors (PRR) on immune cells will provide additional immune stimulation [49]. The result of cell experiments showed that the absorption of CPMV-conjugated NY-ESO-1TMR was observed to be significantly higher than unconjugated NY-ESO-1TMR, proving that CPMV is a stronger epitope delivery to APC. Moreover, the detection of cytokine levels in mouse BMDC showed that the combination of soluble peptide antigen NY-ESO-1 vaccine and adjuvant can initiate cell immunity that presents antigen to APC, and CPMV vector vaccine activates APC effectiveness has a further significant improvement in statistics. Further analysis of $CD8^+$ T cells in the mouse spleen showed that the CPMV-NY-ESO-1 vaccine produced a more effective $CD8^+$ T cell immune response and thus improved the specificity of the original vaccine compared to single nucleotide plus adjuvants [50]. The results of this study still fully illustrated the broad prospects of the target based on NY-ESO-1 and the importance of developing different carriers to enhance immune specificity with improvement of delivery strategy, while further experiments can also focus on using the same delivery platform loaded with other antigen peptide sequences such as NY-ESO-180-109, 20-mer NY-ESO-191-110, or further immono responses, as NY-ESO-1 antigen can also induce a humoral immune response [49]. Studies on tumor mRNA have shown that NY-ESO-1 can induce B cells to produce IgG by using SEREX technology to analyze [43], and clinical reports have also shown that various cancers will have different levels of humoral immune response to NY-ESO-1 targets in different cancers [50], which makes us expect that NY-ESO-1 targeting methods could play a vital role in TNBC treatment.

5.2 Clinical trials of CTA vaccine

Currently, seldom of the CTA-targeting vaccines have been approved for marketing. However, the first clinical trial of CTA-targeting vaccine for cancer treatment was carried out more than a decade ago. A total of 50 immunotherapies have been approved for clinical trials for different NY-ESO-1 targets so far, of which 12 are active and 31 are recruiting volunteers. Meanwhile, there are a total of

27 vaccine therapies targeting MAGE targets. Among them, 18 have been completed and 8 have resulted [45].

However, none of these clinical trials are used for the treatment of TNBC. In one of the clinical studies on lung cancer with the MAGE-A3 target, it was observed that with the co-stimulation of autologous T cells and Poly-ICLC, the combination of MAGE-A3 vaccine triggered by GM-CSF produced a high frequency of vaccine-specific T cell responses after transplantation [51]. In another set of phase II clinical comparative trials, the vaccine trial reached the primary endpoint of safety and tolerability. Patients vaccinated with DC or Montanide had significant antibody titers to the NY-ESO-1 immune antigen [50]. Therefore, considering the good prognosis of the treatment to other cancers with a similar mechanism, we hold an optimistic attitude about the application of CTA-targeting vaccine therapy in the treatment of TNBC, and hope to see the conduction of any clinical trials of CTA-targeting vaccine therapy that is dedicated to TNBC. Here, two undergoing selected clinical trials of CTA-targeted vaccines were completed at I/II phase (NCT01245673, NCT02334735), respective resulting were shown that 76% of patients generated T-cell response, with an overall survival rate in 2-year of 74%, and a 2-year event-free survival rate of 56%, while the latter preliminary data show that subjects in both arms develop T cell responses to both antigens. [50][52]

5.3 Future prospect

It can be seen that CTA provides a wide variety of specific antigen targets for cancer vaccine therapy. Therefore, in some future designs, we can see a large number of cocktail therapies that use multiple antigens synergistically, or even multiple methods. At the same time, most of the CTA vaccines currently entering clinical trials are peptide and DC vaccines. For example, the improvement of the delivery strategy of Patel and others above will greatly improve the efficiency of delivery, increase the specific activation degree of APC, and thereby enhance the accuracy of targeting. On this occasion, we believe that the use of mRNA vaccines-as stated by Kariko and Weissman, mRNA vaccines have absolute advantages in terms of safety, activation efficiency of cellular immunity, and the persistence of suppressing cancer recurrence, so they are bound to be an improvement direction [10].

In the process of treating metastasis, CTA-targeting vaccines have presented a complicated but hopeful situation. Among the CTA vaccines currently undergoing clinical trials, there is a phase II trial against metastatic melanoma, which can be said to have a unique prospect in general [49]. However, in a case study, a melanoma patient (NY-ESO-1 positive) was vaccinated with the NY-ESO-1 vaccine. Although the patient's immune response was activated in a short term, fatal, inoperable brain metastasis was quickly screened after his death in just 6 years, and the metastasis is negative for NY-ESO-1, indicating that cancer control and cancer escape in this patient were governed by NY-ESO-1-specific immunological pressure, and there is likely to be immune editing and immune escape at the tumor site [53]. Meanwhile, novel articles have reported that in TNBC, the neoantigen SP17 which belongs to the CTA family, presents the character of highly related with metastasis, highly conserved in primary and metastatic tumor cells, and not expressed in normal breast cells. This allows SP17-targeted vaccine therapy to produce anti-tumor cell immunity that can eradicate cancer cells, and also interfere with the basic mechanisms involved in SP17-mediated cancer cell survival, metastasis, and drug resistance [54], which provides an important novel target in treating against metastasis of TNBC. In summary, in terms of anti-metastasis, targets with strong specificity, high degree of conservation, and not easy to escape immune surveillance are the most ideal targets, while comprehensively studied targets might face the issue of immunoediting and immune escape, leaving a greater pressure not only on the development of vaccines, but also on the screening of novel antigens.

Besides, since the method of vaccine therapy has been put into clinical trials for a short time, it is still impossible to confirm the clinical improvement direction of the CTA vaccine, such as whether it will produce mutations. We believe that further studies are needed for investigating the role of CTA in tumor cells, including the various signaling pathways involved, to help us better understand the mechanisms involved in treatment.

6. Conclusion

This review discussed that despite the lack of typical targeting targets such as ER/PR or HER2, popular targets represented by Frα, CTA and MUC1 in TNBC, still have broad prospects for vaccine therapy, which can be an efficient and specific way to achieve the effect of immunotherapy and has a unique characteristic to resist metastasis. Although currently, vaccine therapy has not shown very satisfactory results in treatment, we believe that with much in-depth study induced, vaccine therapy is still promising to become an important solution for TNBC. Represented by these three targets, although the prospects of TNBC vaccine therapy are complex, they all have certain clinical application possibilities. We suggest that more excellent delivery strategies and more suitable adjuvants should be developed in the future to improve the overall delivery efficiency and actively cooperate with experiments such as cocktail therapy. In general, vaccine therapy has broad prospects in treating TNBC.

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