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The Mechanism of T Cells in the Microenvironment of Triple Negative Breast Cancer and the Application Potential of Immunotherapy

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Abstract. Triple negative BC (TNBC) is a malignant tumor with high invasion, high incidence rate and poor prognosis. The mechanism of T cells in its microenvironment and the potential application of immunotherapy have become the focus of current research. Research has shown that the tumor microenvironment of TNBC is highly heterogeneous, and T cells, as core members of the immune system, play a crucial role in the anti-tumor process by recognizing and clearing tumor cells. However, T cell activity is often suppressed by ICs such as PD-1/PD-L1, leading to tumor immune escape. With the development of single-cell RNA sequencing technology, there is a deeper understanding of the functional status of T cells in the TNBC microenvironment. Meanwhile, IC inhibitors (ICIs) and adoptive cell immunotherapy have shown significant potential in the treatment of TNBC. For example, PD-1 inhibitors combined with chemotherapy significantly prolonged the lifespan of TNBC patients. The results of this study reveal that the activation of T cells in the TNBC microenvironment is closely related to tumor prognosis, and immunotherapy can improve the therapeutic effect of TNBC patients by regulating T cell activity. The research significance lies in providing new strategies for the precise treatment of TNBC, especially the broad application prospects of immunotherapy. In the future outlook, with the deepening understanding of the molecular mechanism and immune microenvironment of TNBC, as well as the development of new immunotherapy drugs, the prognosis of TNBC patients is expected to further improve, achieving more personalized and effective treatment plans.

Keywords: Triple-negative breast cancer; T cell; specific antibody; immunotherapy; combined therapy.

1. Introduction

The concept of the tumor microenvironment (TME) refers to the microenvironment composed of cells, blood vessels, extracellular matrix, immune cells and other components around tumor cells.TME is mainly composed of the extracellular matrix, fibroblasts, myofibroblasts, neuroendocrine cells, adipocytes, immune and inflammatory cells, and blood and lymphatic vascular networks [1]. T lymphocytes, B lymphocytes and other macrophages are constituent cells of the tumor microenvironment. T cells are one of the important members of the tumor immune microenvironment. As an important cell of the human immune system, T cells have anti-tumor effects. They play an important anti-tumor role by identifying and killing tumor cells. The incidence rate of BC ranks first among female malignant tumors in the world, seriously endangering women's health; In China, the incidence rate of female BC is also increasing year by year. According to the data released by the International Cancer Research Center of the World Health Organization, it is estimated that in 2018, there were about 2.08 million newly diagnosed cases of female BC in the world, with 626000 deaths, an increase of 18.6% over the newly diagnosed cases in 2012, and the number of deaths increased by 16.6%. TNBC accounts for 12%~20% of the new cases of BC every year. In China, BC ranks first in female cancer incidence and fifth in female cancer death [2]. With the development of early diagnosis and comprehensive treatment, the mortality of BC has gradually declined. Triple-negative breast cancer (TNBC), as an aggressive tumor, has accounted for nearly one-fifth of all breast cancers (bc),

and the experimental and clinical results are poor, and there is no effective treatment with special efficacy. To date, chemotherapy remains the standard treatment for patients with metastatic triple negative cancer (mTNBC), but long-term outcomes are not ideal [3]. Different from traditional treatments such as radiotherapy and chemotherapy, which directly kill tumor cells, the basic principle of immunotherapy is to stimulate the body's own anti-tumor immune response, and use the body's own immune response to clear tumor cells, so as to treat the corresponding cancer. Moreover, compared with traditional therapy, immunotherapy has the advantages of high specificity, less damage to normal tissue, and immune memory can be generated in some patients after treatment, thus further reducing tumor recurrence. This study aims to further understand the mechanism of T cells in the microenvironment of triple negative BC, so as to improve the effect of immunotherapy. In addition, this study also aims to introduce the application prospects and potential risks of different immunotherapy strategies in BC.

2. Background of Triple Negative BC Treatment

BC is a common malignant tumor, which has an important impact on women's health.Breast tumors is an extremely frequent cancer among women internationally, affecting around two million newly diagnosed cases and 600,000 deaths yearly. TNBC, which makes up 10% to 20% of all BCs, is becoming increasingly prevalent in women under 40 [4]. In China, the incidence rate of BC is increasing year by year, which indicates that BC has become one of the important issues for women's health. According to statistics, more than 200000 new cases of BC are diagnosed every year in China. BC has become the most common malignant tumor, and more and more Chinese women have detected BC in the physical examination report. Behind this phenomenon, it is not only related to factors such as population aging and environmental pollution, but also closely related to lifestyle and genetic factors related to BC. However, it is worth noting that the treatment methods and effects of BC are constantly improving, and many BC patients can obtain good survival rate and quality of life. With the development of early diagnosis and comprehensive treatment, the mortality of BC has gradually decreased [5].

BC is a kind of tumor with high heterogeneity at the molecular level. According to the expression of many molecules in BC, including estrogen receptor (ER), progesterone (PR), and Kiel-67 Antigen (Ki-67) proliferation index, St. Gallen BC Conference classified BC into lumen type A, lumen type B1, lumen type B2, HER2 positive and TNBC [6]. TNBC is a special type of BC, which is different from other BC clinically. For example, TNBC does not express ER, PR and HER2, three important indicators. The non expression of these three important indicators leads to the biological behavior of TNBC is different from other types of BC [7]. Moreover, TNBC is more common in young women and has a higher degree of malignancy and recurrence rate. Because it is not affected by hormone therapy and some currently known targeted therapies, it makes treatment more challenging than other types of BC. There are still some challenges in the treatment of TNBC. Traditional treatment methods, such as surgery, radiation therapy, and chemotherapy, are the basic means of treating TNBC. Among them, radiotherapy and chemotherapy remain the main treatment methods for TNBC. However, these treatment methods often cannot meet the needs of all patients, so it is necessary to constantly explore and develop new treatment strategies. With the development of science and technology, in recent years, many research focuses have been placed on the fields of immunotherapy and targeted therapy. These new treatment strategies have brought new hope and opportunities to patients with TNBC. This article will focus on the role of T cells in the microenvironment of BC and the potential application of immunotherapy.

3. BC Immunotherapy

BC immunotherapy involves activating the patient's own immune system to attack and suppress the growth and spread of BC cells. Compared with traditional chemotherapy and radiotherapy, immunotherapy has many advantages, such as fewer side effects, more selective to tumor cells, and

long-lasting. For this reason, scientists now consider immunotherapy an extremely important breakthrough in the treatment of BC [8,9].

As mentioned above, the core mechanism of immunotherapy is to attack BC cells by activating T cells in the immune system, as well as other immune cells by recognizing and locking on to specific antigens on the surface of BC cells, releasing cytotoxins or regulatory factors, thereby destroying cancer cells and triggering further responses from the immune system. TNBC immunotherapy can be broadly divided into the following categories: Active therapy based on cancer vaccines (CVs) and ICIs, ICIs consists of monoclonal antibody based passive therapy, adoptive cellular immunotherapy, oncoytic viruses (OVs) and non-specific immunostimulatory therapy (cytokine therapy).

3.1. Tumor Vaccine

With the progress of medical science and technology, BC vaccine has gradually become a research hotspot and a topic in clinical field. The BC tumor vaccine suppresses or kills BC cells by stimulating the body's immune system to produce a specific immune response. The core principle is that the vaccine causes the body's immune system to actively recognize and attack BC cells, thereby reducing the number of BC cells [10]. Compared with radiotherapy and chemotherapy, tumor vaccine is less harmful to human body, has weak adverse reactions, and has high specificity, and theoretically has better therapeutic effect. However, the actual situation is that vaccine development is difficult, and the existing technology is limited, resulting in poor clinical effect. It is currently classified as tumor-specific antigen (TSA), such as New York esophageal squamous cell carcinoma 1, NY-ESO-1), sperm protein 17 (SP17), insulin-like growth factor 1 receptor (IGF-1R), α-whey protein, and neoantigen related vaccines such as dendritic cell (DC) vaccines [11]. In the past two decades, BC vaccines have not brought significant clinical benefits, and only a few BC vaccines have entered phase III clinical trials. To improve the effectiveness of the TNBC vaccine, researchers are turning to a combination treatment strategy of the vaccine and ICIs. At the same time, tumor cell vaccines and DC vaccines based on emerging technologies such as liposomes and engineered exosomes show good anti-tumor activity in TNBC animal models, and are expected to enter clinical studies in the next step [12].

3.2. ICIs

Regarding immune checkpoints, studies have shown that a group of adaptive immune system regulatory points with a large range can play a role in the degree of self-tolerance and anti-tumor immunity. Physiologically, these checkpoints regulate the positive or negative nature of the immune response, coordinating the intensity and type of response [13]. As a means of immunotherapy, the main principle of ICIs is to restore the activity of the patient's immune system by inhibiting the immunosuppressive signals in the BC cells and TME, so that the patient's immune system can better fight against cancer. In the case of BC cells, they can suppress the activity of immune cells by activating IC molecules, thereby evading immune surveillance. ICIs can block the signaling of these IC molecules, activate immune cells, and enhance their ability to attack BC cells. Studies have shown that in some BC patients, ICIs can significantly improve patient survival and treatment outcomes for advanced BC. These drugs can be used not only alone, but also in combination with conventional treatments such as chemotherapy and radiotherapy to work synergistically. Clinical studies have shown that ICIs not only have a certain effect on TNBC, but also have a positive therapeutic effect on hormone receptor-positive and HER2-positive BC. There are currently several PD 1, PDCD1, CTLA4 or. Antibodies to the PD-1 /PD-L1 pathway are approved for use in many tumors. A large number of targets for other novel ICs (such as T cell immunoreceptors with Ig and ITIM domains, TIGIT, V-set immunoregulatory receptor etc.) are in the stage of clinical trials and preclinical development [14]. PD-1/PD-L1 are the classic immunomodulatory checkpoints. PD-1, a member of the CD28 family, was first identified in the programmed death process of two cell lines, 2B4.11 and LyD9, hence the name programmed death receptor 1. It is widely expressed in activated B cells, T cells, monocytes and regulatory T cells. PD-1 binding to its ligands (PD-L1 and PD-L2) can induce

T cell dysfunction, leading to tumor immune escape. PD-L1 is an immunomodulatory molecule of the B7 family (B7 homolog 1, B7-H1), which has a positive immune stimulation effect. Overexpression of PD-L1 in BC cells causes it to bind to PD-1, resulting in enhanced Treg activity while disabling activated CTL and mediating immune escape [15]. A large number of studies have shown that if PD-1/PD-L1 inhibitors are used in clinical treatment, cancer with CD8 + T cells will have better clinical performance, which can be used as a predictive and therapeutic biomarker of anti-PD-1 therapy [16]. At present, PD-1 and PD-L1 inhibitors have been widely used in the treatment of advanced cancer, but the efficacy is not obvious when used alone, and the expression of PD-L1 in tumor cells and immune infiltration is different in different core sites in different parts of the same tumor, which indicates that a single biopsy may not represent the entire PD-L1 state. Further study of the relationship between tumor and immune matrix PD-L1 expression levels and clinical response to PD-L1 inhibition will be critical, especially in high-grade tumors with hormone receptor negative [17].

3.3. Adoptive Cellular Immunotherapy

Adoptive cell therapy (ACT) is an emerging tumor immunotherapy approach that has attracted widespread attention in the treatment of BC in recent years. In particular, chimeric antigen receptor engineered T cells (CAR-T) therapy. The treatment uses the patient's own immune cells, which are extracted, cultured, modified and re-transfused to enhance the immune system's ability to fight malignant tumors.

The therapeutic principle of secondary cellular immunotherapy is based on the activity and specificity of immune cells. First, doctors extract immune cells from the patient, such as T lymphocytes, and then grow and modify them in vitro to make them more capable of attacking malignant tumor cells. These modified immune cells are reinjected back into the patient to fight the tumor cells. In this process, immune cells can recognize and attack tumor cells, causing them to lose their ability to grow and spread. CAR-T cells are genetically modified to allow patient T cells to express CAR, and CAR-modified T cells can specifically recognize tumor-associated antigen (TAA), making effector T cells more targeted, lethal and durable than immune cells used in conventional applications [18]. For TNBC, Chen Yue et al. have used ROR1 CAR-T constructed to find that interferon-γ released in the CAR-T group can be used against the positive target cell MDA-MB-231 under the condition of 2: 1, 4: 1, 8:1 efficacy target ratio. IFN-γ) were higher than control group. However, after co-culture of CAR-T with negative target cells, IFN-γ was almost not released, even at high efficiency target ratio (8:1), and the production of lactate dehydrogenase (LDH) was less. It has been proved that ROR1 CAR-T has a specific killing effect on ROR1-positive TNBC cells, and the risk of off-target is small [19]. At present, anti-TNBC studies in the field of CAR-T cells are mostly in the pre-clinical research stage, and the main targets and anti-tumor activities are shown in Table 1.

Table 1. Target and activity of CAR T cells against TNBC [20]

Target point	Target type	Anti-TNBC activity
AXL	Receptor tyrosine kinase	AXL-CAR T cells inhibited the growth of TNBC xenografted tumor mice and improved the survival rate of TNBC xenografted tumor mice
CD32A	Fγrii cell surface glycoprotein	CD32A-CAR T cells combined with cetuximab or panizumab can eliminate TNBC cells and inhibit the secretion of IFN-γ and TNF-α in vitro
GD2	bissialoganglioside	GD2-CAR T cells inhibited tumor growth in situ and distant lung metastasis in TNBC xenografted tumor mice
Mesothelin	Cell surface glycoproteins	Mesothelin-car T cells killed TNBC cells by increasing the expression of perforin and granzyme B
CSPG4	Cell surface glycoproteins	CD28 co-stimulated CSPG4-CAR T cells inhibited the growth of TNBC and inhibited tumor angiogenesis in vivo and in vitro
MUC1	Cell surface glycoproteins	MUC1-CAR T cells inhibited the growth of TNBC cells by enhancing the expression of Th1 cytokines and chemokines
ROR1	Tyrosine kinase receptor	ROR1-CAR T cells in combination with SD-208 inhibit TNBC cell growth through TGF-β receptor pathway

At present, the research of adoptive cellular immunotherapy related to BC is progressing rapidly. Scientists are constantly exploring ways to improve the effectiveness and safety of this treatment. For example, some studies have focused on finding more lethal subpopulations of immune cells, such as specific cell lines (TILs). These modified immune cells are better able to recognize and attack malignant tumor cells, thus improving treatment effectiveness.

3.4. Oncolytic Virus

As a plague virus, oncolytic virus can selectively attack cancer cells. On the one hand, oncolytic viruses can enter the inside of cancer cells through specific receptors, and replicate and spread inside them, eventually leading to the dissolution of cancer cells. On the other hand, oncolytic viruses can activate the body's immune system and enhance the killing effect on cancer cells. This dual mechanism makes oncolytic virus have better therapeutic effect and safety. In TNBC treatment, the application of oncolytic virus has made a certain breakthrough. The study showed that by modifying the genome of the oncolytic virus, it could be made to better target BC cells while reducing the damage to normal cells. In addition, oncolytic virus can also be combined with other therapeutic means, such as chemotherapy drugs, immunotherapy, etc., so as to achieve synergistic enhancement of therapeutic effect. The combination of oncolytic virus and chemotherapy also has a good therapeutic effect in clinical trials, and some cancers such as lung cancer show a high response rate to ICIs, and the treatment effect is good, often referred to as "hot tumors". However, BC, as a "cold tumor", does not respond well to this therapy, and oncolytic virus may make the "cold" tumor become "hot" by reprogramming the cold TME, ultimately making patients more sensitive to other immunotherapies [21]. OVs can be divided into DNA virus and RNA virus according to the different genetic material of OVS genome. Common DNA viruses include oncolyticadenoviruse (oAd), oncolyticherpessimplex virus (oHSV), oncolyticvaccinia virus, etc [22].

3.5. Non-Sapecific Immunostimulation Therapy (Cytokine Therapy)

In theory, cytokine therapy uses cytokines produced in an organism to regulate and influence the immune system to enhance the body's ability to fight tumors. In the treatment of BC, cytokine therapy mainly includes immune cytokines and tumor cytokines. Immune cytokines can activate the activity of immune cells in the body and enhance the attack force of the immune system, thus inhibiting the growth and spread of BC cells. However, tumor cytokines can directly act on BC cells, promote their apoptosis and anti-proliferation, so as to achieve the therapeutic effect. TNF-α is an important mediator produced by mononuclear macrophages, which can effectively regulate the inflammatory environment in the body of patients. IL-6 can effectively release a large number of inflammatory mediators, which are mainly produced by lymphocytes and endothelial cells, and fully regulate the immune activity of mononuclear macrophages, B lymphocytes and T lymphocytes, and can also participate in the formation of various immunopathology [23]. The study found that IL-6 and TNF-α had statistical significance with tumor size and clinical stage of BC, and the level of T4 patients was significantly higher than that of T1-T3 patients, but there was no statistical significance between T1, T2 and T3 patients. Some studies have suggested that IL-6 may enhance the expression of cyclin cyclinD1, change the balance of proliferation/apoptosis, and promote the proliferation and growth of tumors. It is also believed that IL-6 can promote the efficiency of energy metabolism of tumor cells and further increase the rate of tumor division and growth [24]. At present, cytokine therapy has great application potential, but the number of cases observed and analyzed is limited, and relevant cases and clinical data need to be collected in the future, as well as long-term research and discovery.

4. Combination Therapy

As mentioned above, no matter what kind of immunotherapy, the effect of single immunotherapy is not ideal, so for TNBC, the combination therapy program with immunotherapy as the main treatment and other therapies as the auxiliary therapy has the most therapeutic potential. Combined therapy refers to the simultaneous use of surgery, radiotherapy, chemotherapy, targeted therapy, immunotherapy and other methods in the treatment of BC, in order to achieve better treatment effects and improve the survival rate. Various treatment methods complement each other and organically combine together, making the treatment of BC more comprehensive, individual and accurate, rather than just the simple superposition of various treatment methods. By means of pathological classification, molecular phenotype, gene detection, etc., the most suitable treatment plan can be formulated according to the specific conditions of patients. This can avoid ineffective treatment, reduce unnecessary side effects and pain, and improve the success rate of treatment and quality of life.

For BC, given the unsatisfactory efficacy of single agents, immunotherapy for BC focuses more on combination strategies, including combination chemotherapy, targeted therapy, and local radiotherapy to reverse the "cold tumor" state of BC. For example, ICD inducer combined with ICI could enhance the infiltration of immune cells while maintaining its anti-tumor function. ICI combined with TGF-β antibody helps drugs penetrate into tumors. bispecific antibodie (BsAb) targets both immune cells and tumor cell markers, thereby assisting immune cells to approach and kill tumor cells [25]. Chemotherapy has different effects on the immune response because of different drugs, doses, and duration of chemotherapy, and is also associated with different types of immunotherapy. Many trials are considering combining chemotherapy on the basis of PD-1/PD-L1 blocked immunotherapy for combination therapy, with the aim of enhancing immune priming through antigen release and DC regulation, or enhancing immunity by easing immunosuppressive signaling in TME [26]. paclitaxel (PTX), is the main taxane drug for the treatment of BC, Although widely used, paclitaxel has poor pharmacokinetic characteristics and low therapeutic efficacy due to its poor solubility in water. Paclitaxel is often used in combination with other drugs to treat BC, such as Apatinib combined with paclitaxel for injection in advanced BC. Since the progress of immunotherapy, researchers have tried to combine paclitaxel with immunotherapy. A series of clinical studies have been conducted on PD-1/ PD-L1 inhibitors in advanced TNBC, either

monotherapy or in combination with chemotherapy. The IMpassion 130 trial established the foundation for the most recent marketing authorization of atezolizumab in advanced TNBC. Over 900 patients with incurable TNBC who had relapsed 12 months or more after adjuvant chemotherapy been randomly randomly assigned to receive either nab-paclitaxel plus atezolizumab (a PD-L1 inhibitor) or nab-paclitaxel and placebo in the third phase of registry study IMpassion 130.[27] The findings of this study were cited and recommended in international guidelines.The results of the IMpassion130 trial demonstrate that BC is about to enter the era of immunotherapy. As atezolizumab, an anti-PD-L1 pharmaceuticals, is introduced in addition to the initial course of treatment with nab-paclitaxel for patients with PD-L1-positive metastatic or inoperable locally advanced TNBC, Schmid et al. exhibit a substantial increase in overall survival (OS).[28]. With the continuous improvement of understanding of immunotherapy, in addition to combination chemotherapy, ICIs combined with radiotherapy and targeted drugs in the treatment of advanced TNBC also showed initial efficacy. Although the combination therapy has made remarkable progress in the treatment of BC, there are still some controversies and challenges. Different patients have different conditions and responses to treatment, so more in-depth research and clinical practice are needed to optimize and improve combination treatment strategies. At the same time, most of the combination therapy is the interaction of drugs, chemoradiotherapy and ICIs, and other immunotherapy methods such as tumor vaccines have made little progress, and further research and clinical experiments are still needed

5. Conclusion

Compared with traditional radiotherapy, chemotherapy and other treatment methods, immunotherapy can identify and attack tumor cells without causing too much damage to normal cells. Simply put, it is to strengthen the body's own immune system, which compared with the broad spectrum of chemotherapy and radiotherapy, can greatly reduce the side effects of patients in the treatment process and improve the quality of life of patients. While traditional treatments often develop resistance or relapse after a period of time, immunotherapy works by activating the immune system to fight tumors, and the effects of the body's own antibodies and T cells can persist in the body for a long time, helping to prevent the risk of recurrence. In addition, immunotherapy can complement other treatment methods, that is, combination therapy, which can effectively solve the problem of poor effect of single immunotherapy, further improve the efficacy, and reduce the course of treatment, produce a variety of treatment plans, with broad treatment prospects.

However, immunotherapy has some drawbacks and limitations in the treatment of BC. For example, the scope of immunotherapy is relatively narrow. Current immunotherapy approaches, which focus on specific BC subtypes, namely HER2-positive and TNBC, are relatively ineffective in treating hormone-positive BC and may not be as effective as traditional treatment options such as surgery. For example, immunotherapy may have immune-related side effects in some patients. The principle of immunotherapy is to attack tumor cells by activating and strengthening the immune system, but this can also cause the patient's immune system to overactivate, triggering a series of uncomfortable reactions, such as fatigue, immune suppression and so on. The adverse reactions of immunotherapy drugs are different from those of traditional chemotherapy drugs. The adverse reactions may not be recognized in a short period of time, but once they occur, they may affect the physical functions of patients for a long time. Therefore, clinicians need to have rich experience in judging the adverse reactions caused by immunotherapy and give timely treatment to reduce the incidence of serious immune-related adverse reactions. In addition, the high cost of immunotherapy is also a problem that cannot be ignored. The cost of immunotherapy is high compared to traditional treatments, which can be a burden for some patients.

For TNBC, we also need more clinical trials and clinical data to validate the efficacy and safety of immunotherapy and combination therapy. In cutting-edge scientific research, we also need to deeply study the molecular mechanism of TNBC in order to develop more excellent and convenient treatment methods through molecular theory. There is also the development of other integrated

treatment strategies, such as the combination of immunotherapy with traditional treatment means, which helps to improve the therapeutic effect and clinical experience of TNBC patients.

Authors Contribution

All the authors contributed equally and their names were listed in alphabetical order.

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