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Role and Challenges of Adoptive Cell Therapy Based on Tumor Infiltrating Lymphocytes in Triple-negative Breast Cancer

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Abstract: Adoptive cell therapy (ACT) based on tumor infiltrating lymphocytes (TILs) is a key branch of tumor immunotherapy. Currently, it has been very effective in the diagnosis and treatment of melanoma and has also shown great potential in the diagnosis and treatment of other solid tumors. This article focuses on the application of this therapy in the diagnosis and treatment of triple-negative breast cancer (TNBC). In the diagnosis and treatment of TNBC, there is a problem of immune escape of tumor cells caused by TEX, which seriously affects the treatment effect and requires in-depth analysis. At the same time, TILs in the tumor immune microenvironment (TIME) are related to the direction of treatment. This article takes the immune escape mechanism of T cell exhaustion (TEX) as an entry point to analyze the clinical progress and challenges of TILs-based ACT in the diagnosis and treatment of TNBC, which is of great significance. The research results found that ACT based on TILs has shown the potential to significantly improve TIME and enhance immune function in the treatment of TNBC, find a way to optimize the TNBC diagnosis and treatment plan, cleverly integrate ACT with traditional diagnosis and treatment methods, and enhance the effectiveness and safety of the diagnosis and treatment plan.

Keywords: Tumor infiltrating lymphocytes, adoptive cell therapy, T cell exhaustion, immune escape, triple-negative breast cancer.

1. Introduction

TNBC is a special subtype of invasive breast cancer (BC), accounting for approximately 10.0% to 20.8% of all BC cases [1]. Due to the lack of these common therapeutic targets, TNBC patients have relatively limited treatment options, and traditional treatments are not effective for them. At the same time, TNBC is usually more invasive, with a higher recurrence rate and metastasis risk, and the prognosis of patients is relatively poor, which poses a huge challenge to clinical treatment [1]. However, TNBC has a high level of TILs in its tumor microenvironment (TME). Therefore, TILs-based immunotherapy has a natural advantage for TNBC. The study of TILs-based ACT in TNBC will provide reference and inspiration for immunotherapy research of other types of cancer. In clinical practice, TILs-based ACT is expected to become a new and effective treatment method, bringing new hope to patients.

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Improving the efficacy and safety of this therapy through a series of scientific and effective measures is of great significance to patients. When the efficacy of therapy is improved, it can more effectively relieve patients' pain and reduce the physical and psychological torment of symptoms, thereby significantly improving the patient's quality of life. At the same time, improved safety can reduce the risks and adverse reactions that patients may face during treatment, making the treatment process smoother. This kind of improvement and optimization of therapy has a value that cannot be ignored in clinical application. It can provide medical workers with more powerful treatment methods and help more patients overcome the disease. By exploring the role of TILs-based ACT in TNBC, we explore that TILs-based ACT can improve TIME and enhance immune function in TNBC patients. TILs affect the composition and function of immune cells in the TME, regulate the balance of immunosuppressive factors and cytokines, thereby improving the overall TIME and enhancing the body's anti-tumor immune function [2].

2. TILs can Effectively Inhibit Tumor Cell Immune Escape

2.1. T cell exhaustion (TEX)

TEX refers to a state in which T cells are stimulated by antigens for a long time and gradually lose their functional activity. TEX usually occurs in TME, chronic viral infections and autoimmune diseases. The generation of TEX mainly includes the following reasons. Continuous stimulation of antigens will not only cause T cells to gradually lose their effector function, but also increase the expression of co-inhibitory receptors such as PD-1 and LAG-3. These receptors release inhibitory signals after binding to specific receptors, which will further inhibit the function of T cells [3,4].

At the same time, there are a variety of immunosuppressive factors in TME, such as regulatory T cells, TGF-β, IL-10, etc. Immunosuppressive cells, metabolic inhibitors and inhibitory cytokines work together to further aggravate TEX [5]. On the other hand, T cells require a lot of energy and nutrients during activation and proliferation, and the proliferation and metabolism of tumors in the TME can affect the metabolic state of T cells and thus their function.

2.2. TEX triggers immune escape

TEXs are characterized by increased expression of immunosuppressive receptors, weakened effector functions, decreased self-renewal capacity, and altered epigenetics, transcriptional programs, and metabolism. This state leads to tumor immune escape, creating a favorable environment for tumor development and metastasis [6]. The ability of exhausted T cells to produce IFN-γ, TNF-α, etc. is significantly reduced, weakening the killing effect of T cells on tumor cells [6].

2.3. Role of TILs in immune escape

The expression of HLA-I molecules in BC and its relationship with TILs density were detected by immunohistochemistry. It was found that in BC, the retention of HLA-I molecules was significantly related to high TILs density, while the loss of HLA-I was One of the main causes of immune escape [7]. However, studies have found that not all TILs block immune escape, and different TILs subsets play different roles in immune escape. For example, CD8+ T cells usually have anti-tumor activity, while Treg cells promote tumor growth and escape by proliferating and inhibiting the function of effector T cells [8,9]. Therefore, amplifying specific TILs subsets can effectively inhibit the immune escape of tumor cells.

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3. Role of TILs in TME

3.1. Immune Response and Immunoregulatory Effects of TILs

CD8+ T cells in the TILs subset can recognize and bind to specific sites on the surface of tumor cells, and directly kill tumor cells by releasing effector molecules such as perforin and granzyme to induce apoptosis or necrosis of tumor cells [2]. TILs can also enhance the activity of other immune cells (such as natural killer cells, macrophages, etc.) by secreting cytokines (such as IFN-γ, TNF-α, etc.), further amplifying the effect of the immune response. TILs include not only effector T cells but also Tregs, which help establish immune tolerance to self-antigens and regulate inflammatory responses in the TME by inhibiting the activation of effector T cell growth and proliferation [10].

3.2. TILs can be used as a prognostic marker for various cancers

TILs can be used as a prognostic marker for a variety of cancers, mainly because TILs can effectively reflect the interaction between tumors and TIME on tumor growth, invasion and metastasis. The number of TILs is associated with a good prognosis. A study conducted immunohistochemical tests on 126 TNBC patients and found that high-density TILs were associated with a better prognosis [11]. In addition to the number of TILs, the functional status of TILs also affects good prognosis. Highly active TILs can more effectively identify and kill tumor cells, while functionally exhausted TILs may not be able to work effectively. In non-small cell lung cancer, the number of Granzyme B-positive TILs is associated with a better prognosis, indicating that these cells have stronger anti-tumor activity [12].

3.3. Effect of immunosuppressive status on TILs activity

The immunosuppressive state is an important factor affecting the activity of TILs. Many studies have shown that the immunosuppressive mechanism in the TME can lead to a decrease in the activity of TILs, resulting in functional exhaustion, which in turn affects the effect of immunotherapy. In diffuse large B-cell lymphoma, the exhaustion of CD8+ TILs is a major obstacle. Studies have found that the exhaustion state of CD8+ TILs is heterogeneous and related to clinical prognosis [13]. In gliomas, high cortisol levels in the immunosuppressive TME limit T cell infiltration and lead to failure of immune checkpoint blockade therapy [14]. It can be seen that combining multiple therapies such as immune checkpoint inhibitors (ICIs), low-dose chemotherapy and metabolic regulators to overcome the immunosuppressive state can provide new diagnostic and treatment strategies and directions for future immunotherapy [15,16].

4. TILs in the treatment of TNBC in ACT

4.1. TNBC overview

TNBC accounts for 10.0% to 20.8% of all BC cases. It is a special subtype of invasive BC. The characteristics of TNBC are that its tumor cells do not express estrogen receptors, progesterone receptors, and human epidermal growth factor receptor 2, and are therefore insensitive to traditional endocrine therapy and targeted therapy [1,17]. The complex TME components of TNBC make TNBC extremely clinically heterogeneous, including different genetic variants and molecular subtypes, extremely aggressive and with poor prognosis, which makes its treatment particularly difficult [1].

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4.2. Immune escape of TNBC

TNBC is a highly malignant tumor with a very complex immune escape mechanism. Studies have found that TNBC achieves immune escape mainly through several pathways. First, in terms of the expression of immune checkpoint molecules (ICs), TNBC cells express a large number of ICs such as PD-L1. After these molecules bind to PD-1 on the surface of T cells, they can inhibit the activity of T cells, ultimately allowing tumor cells to avoid the attack of the immune system [18]. Secondly, the formation of an immunosuppressive microenvironment is also a key link. TNBC can recruit and activate immunosuppressive cells such as myeloid-derived suppressor cells and Tregs, construct an immunosuppressive microenvironment, and inhibit anti-tumor immune responses [19,20]. Third, the secretion of extracellular vesicles also plays an important role. TNBC cells secrete extracellular vesicles containing ICs and immune regulatory molecules, further enhancing the ability of tumor cells to escape immune system [21].

4.3. Clinical progress of TILs in the treatment of TNBC

TILs play an important role in the treatment of TNBC in many aspects. As prognostic markers, high density of TILs is closely related to good prognosis of TNBC patients. Multiple studies have shown that patients with high levels of TILs have significantly higher pathological complete response (pCR) rates and longer survival [22,23]. In terms of predicting treatment response, TILs can be a biomarker for predicting patients' response to neoadjuvant chemotherapy (NAC). TNBE patients with higher TILs levels have a better response to NAC and are more likely to be completely cured [22,23]. Another study evaluated TILs levels and found a significant correlation with pathological responses after NAC [23]. TILs can also be used as markers for immunotherapy. TNBE patients with high levels of TILs have better diagnostic and therapeutic effects in ICIs treatment. For example, the application of pembrolizumab combined with chemotherapy in TNBC has shown significant efficacy, and patients with high TILs levels benefit more from it [24,25]. Related studies have shown that TNBC patients with high TILs levels have a higher response rate after ICIs treatment [25]. TILs can also guide treatment options. For TNBC patients with high TILs levels, more aggressive immunotherapy or combined therapy can be used; for patients with low TILs levels, other treatment strategies may need to be considered [24,25].

5. The development potential and future prospects of TIL therapy in the diagnosis and treatment of TNBC

5.1. The development potential of TILs-based ACT in the diagnosis and treatment of TNBC

TILs show great development potential in the diagnosis and treatment of TNBC. From the perspective of immunogenicity and TME, TNBC is one of the most immunogenic BC subtypes, and its TME has a high level of TILs. Therefore, TILs-based immunotherapy has a natural advantage for TNBC [26]. In addition, ICIs also provide theoretical support for TILs immunotherapy. For example, studies have shown that inhibitors such as PD-1/PD-L1 can induce moderate responses in patients with metastatic TNBC, which provides a theoretical basis for the application of TILs in TNBC [27]. At the same time, multiple clinical trials are evaluating the use of ICIs in TNBC, especially the effects of neoadjuvant and adjuvant therapy. Preliminary results show that these therapies can increase pCR and improve survival in some patients, highlighting the potential and application prospects of TILs in the diagnosis and treatment of TNBC, providing new ideas for treatment strategies, and are expected to improve patient treatment outcomes and survival prospects [28].

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5.2. Challenges of TILs-based act in the diagnosis and treatment of TNBC

Although the role of TILs-based immunotherapy in TNBC has been widely recognized, further research is still needed. For example, the TME of TNBC is complex and highly heterogeneous, which makes it very difficult to automatically evaluate whole-slice images. Traditional image processing methods cannot obtain consistent and accurate TIL evaluation [29]. In addition, at present, the predictability of TILs as a biomarker for the improvement of early disease outcomes is still insufficient, and more clinical trials are needed to verify the validity and reliability of TILs as a biomarker [30]. At present, there is a certain degree of heterogeneity in the evaluation methods of TILs, which need to be further standardized to improve the accuracy and repeatability of the evaluation. How to effectively expand TILs to enhance the efficacy of immunotherapy and how to effectively overcome the immunosuppressive effect of TILs in TME require further basic experiments and clinical trials to explore.

6. Conclusion

Through research, it has been found that the immune escape of tumor cells caused by TEX will greatly limit the body's anti-tumor response, and the high density of TILs has a high correlation with the retention of HLA-I molecules, effectively proving that TILs can inhibit the immune escape of tumor cells, at the same time, TILs play a very important role in predicting treatment response, immunotherapy, tumor microenvironment regulation, prognostic markers and other aspects. Through the analysis of the results of this article, it was found that ACT based on TILs is very effective in the treatment of TNBC. It has shown the potential to significantly improve TIME and enhance immune function. The composition and activity of immune cells have been optimized, providing theoretical foundation support for future research on ACT based on TILs. This article did not explore the complex mechanisms of TILs interaction in the TME, nor did it explore the principles of the low relevance of TILs as biomarkers. If ACT based on TILs can be successfully applied, it is expected to change the treatment pattern of TNBC and be combined with traditional surgery, chemotherapy, radiotherapy and other methods to form a more effective comprehensive treatment plan. ACT may become a salvage treatment for patients who cannot undergo surgical resection or are resistant to chemotherapy. By improving the efficacy and safety of this therapy, it can improve patients' quality of life and prolong their survival, which has important clinical application value.

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