Research Status of Immune Microenvironment in Triple Negative Breast Cancer

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Abstract. Triple negative breast cancer (TNBC) is the most aggressive subtype of breast cancer, with limited treatment options and high rates of recurrence and metastasis due to the lack of specific therapeutic targets. The incidence of bone metastases and brain metastases is also high. They are more likely to relapse and have a poor long-term prognosis. The tumor microenvironment (TME) consists of tumor cells, a variety of mesenchymal cells and an extracellular matrix, which together induce tumor proliferation, stimulate angiogenesis, inhibit cell apoptosis and regulate the immune system, thereby blocking TNBC's anti-tumor response and promote TNBC's progression and metastasis. TNBC has unique TME, and TME may be a potential therapeutic target for TNBC. However, the overall pattern of TME phenotypes remains unknown. Because microenvironment cells have dense crosstalk, it is more reasonable to consider them as a whole. This article will review the TME characteristics of TNBC and the latest progress of TNBC microenvironment immunotherapy.

1 Introduction

Breast cancer is a heterogeneous disease, including subtypes with different biological characteristics and unique therapeutic and prognostic characteristics [1]. According to the latest data from global cancer research in 2020, the incidence of breast cancer ranks first among female malignant tumors, and the mortality rate ranks second among cancer-related deaths [2].

In clinic, estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor 2 (HER-2), Ki-67 proliferation index, combined with differences in gene expression profiles, breast cancer was divided into 4 subtypes: (1) luminal A type [luminal A type: ER and/or PR positive, HER-2 negative, Ki-67 low expression]; (2) luminal B type [luminal B: positive ER and/or PR, negative HER-2, high Ki-67 expression; positive ER and/or PR, overexpression or proliferation of HER-2, any level of Ki-67]; (3) HER-2 overexpression type (HER-2 overexpression or proliferation); (4) basal-like, BL: ER, PR, HER-2 negative, CK5/6 positive and/or EGFR positive][[triple negative breast cancer, TNBC: ER and PR were absent and HER-2 negative]] [3-5].

Triple negative breast cancer (TNBC) lacks specific therapeutic targets and has a poor prognosis compared to other subtypes. Tumor cells and their environment are a functional whole. Tumor cells and tumor microenvironment (TME) interact with each other and jointly promote the occurrence and development of tumors. In the past, cancer treatment ideas were mostly confined to the tumor cells themselves, with corresponding drugs being used to kill them. In recent years, people have studied the potential therapeutic value of TME, aiming to change the "soil" environment of tumor cells through TME. Targeting TME also provides a new idea for the diagnosis and treatment of TNBC [6,7].

2 Concept and Composition of TME

TME is composed of tumor cells, surrounding cytoplasmic cells (such as immune cells) or fibrocytes, endothelial and fat cells, extracellular matrix, and signaling molecules (such as cytokines and chemokines). As early as 1889, Paget, the father of modern pathology, proposed the "family and soil theory" that tumor metastasis required the spread of tumor cells (i.e., seeds), as well as an ideal environment and soil for target organs, but there was no significant progress in clarifying the mechanism [8]. 2015, Hoshino [9] confirmed this theory. The study found that the tumor in the process of transfer release millions of carrying protein and genetic contents vesicles named exosome, ensure the target organs provide appropriate TME, exosome trigger the reaction of the target organs such as inflammation and angiogenesis, arrived at target organs to facilitate tumor cells proliferation.

The immune cells in TME are composed of tumor infiltration lymphocytes (TILs), macrophages, neutrophils, myeloid-derived suppressor cells, MDSCs) and dendritic cells (DC) play the role of antigen delivery. Besides immune cells, TME is infiltrated by fibroblasts, vascular endothelial cells and other stromal cells, which constitute the non-immune microenvironment of tumor [10]. Tumor-associated fibroblasts (CAFs) released stromal cell-derived factors and angiogenic cytokines to promote tumor cell growth and neo-vascularization. Vascular endothelial cells

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mainly mediate the generation of blood vessels and jointly facilitate tumor metastasis [11].

3 The Characteristics of the TME

The most significant characteristic of TME is the dynamic change of its components, which is particularly significant in the later stage of tumor progression. In the early stage of tumor formation, TME is an immune-promoting environment with high pro-inflammatory signals, and immune cells tend to exhibit pro-inflammatory phenotypes. During the process of tumor proliferation and metastasis, TME gradually transforms into an immunosuppressive environment with low oxygen, low pH, low glucose concentration, high fatty acid concentration, low amino acid concentration, high adenosine concentration, and high lactic acid concentration, and immune cells tend to exhibit an inhibitory phenotype. Different from other microenvironments in the body, TME changes are mainly dominated by tumor cells rather than the body itself, which is largely out of the control of the body. In such a complex, dynamic and uncontrollable microenvironment, the functions of the different types of tumor cells play is also complex, dynamic, such as the immune cells can differentiate into different phenotype and metabolic characteristics and the subgroup of different functions, respectively, have effect of anti-tumor or promote the tumor, and through its own metabolic further change TME, A complex and precise interaction network is formed [12].

4 TNBC's Traditional Treatment

For surgical treatment, TNBC patients can undergo breast conserving surgery or modified radical surgery at an early stage. Studies have shown that breast conserving surgery is safe and effective for early TNBC patients. Compared with modified radical surgery, breast conserving surgery can significantly shorten postoperative recovery time, reduce surgical complications and improve postoperative quality of life for patients [13].

Adjuvant chemotherapy, the TNBC neoadjuvant therapy still is given priority to with anthracycline-based drugs and yew chemotherapy drugs. Although TNBC chemotherapy sensitivity is high, but easy to relapse, and toxic effects of cytotoxic drugs on the heart are big and has a high incidence of adverse events. The study found that the use of albumin and cases of complete remission rate of taxol group was obviously higher than that of ordinary taxol group. The toxic side effects of albumin paclitaxel are lighter than those of ordinary paclitaxel, and the discovery and application of albumin paclitaxel benefit TNBC patients [14].

Radiotherapy. Studies have shown that postoperative combined radiotherapy can significantly reduce the risk of local recurrence of TNBC [15]. However, due to the inherent therapeutic resistance of TNBC, the complexity of the mechanism network of tumor resistance and the limited effect of single-target sensitizers, the radiotherapy regimen of TNBC remains to be studied [16,17].

In targeted therapy, the bidirectional interaction between tumor cells and TME may promote tumor progression in multiple ways. Tumor cells alter TME to create a suitable living environment, and TME in turn regulate tumor cells to affect the behavior of tumor cells. Therefore, TME as a target can provide a new idea for cancer treatment [18,19]. Due to the heterogeneity of TME in TNBC, therapies targeting other components of TME are also worthy of attention. Multiple clinical trials with small-molecular tyrosine kinase inhibitors targeting VEGF (endothelial growth factor) have also confirmed its safety and efficacy in advanced TNBC [20].

5 TNBC Microenvironmental Immunotherapy

There are two forms of immunotherapy for breast cancer, active and passive. The former is achieved through the application of immunogenic vaccines against tumor antigens to generate anti-tumor immune responses in breast cancer patients. For example, dendritic cell (DC) vaccine, viral vector vaccine and peptide vaccine are all commonly used immunogenic vaccines in clinics [21,22]. Active immunity in the treatment of breast cancer is mainly targeted at patients with HER-2 overexpression. Passive immunity is the introduction of an exogenous immune effector into the body to generate an immune response to achieve anti-tumor effects. Commonly used immune effector substances include HER-2, MUC1 monoclonal antibody, PD-L1 inhibitors, cytokines (interferon, interleukin, tumor necrosis factor, etc.) and adoptive cell immunotherapy [23].

5.1 Immunomonitoring Site Inhibitor Therapy

TNBC evolution with significant fibrosis and inflammation suggests cancer genome variation not only by internal autonomous mechanism drive the malignant cell growth, but also through the regulation of cancer cells secrete factors related to reshaping the tumor microenvironment, malignant biological behaviors of cancer cells to provide appropriate "soil" [24], similar to another solid tumor, TNBC can promote inflammation in cancer tissues through its own metabolic and functional remodeling, and form a special immune microenvironment [25].

Due to the dispersion of TNBC gene variation spectrum and the high heterogeneity of immune microenvironment, there is no clear and universal therapeutic target at present. The success of novel immune monitoring site inhibitors in the treatment of multiple solid tumors brings new hope for TNBC immunotherapy or combined chemotherapy. Preliminary results of the latest Phase III clinical trial (IMpassion130, NCT02425891) [26]: 902 TNBC patients over 18 years old who developed metastasis and did
not receive chemotherapy or targeted therapy (more than 1 year after radiotherapy and chemotherapy) were randomly assigned to receive anti-PD-L1 monoclonal antibody (atzumab, atezolizumab) in combination with albumin paclitaxel or placebo plus paclitaxel. In PD-L1 positive metastatic TNBC, anti-PD-L1 monoclonal antibody combined with albumin paclitaxel significantly extended disease-free survival (7.5 months vs 5.0 months) and overall survival (25 months vs 15.5 months), with manageable side effects, compared with controls.

5.2 CAFs Remodeled Immune Microenvironment Therapy

Oncogene activation or suppressor gene inactivation not only directly reshaped immune cells in the microenvironment by regulating secreted factors related to cancer cells through intrinsic mechanisms, but also activated mesenchymal fibroblasts, making them CAFs with stable phenotypes. On the one hand, CAFs secrete unique cytokines and chemokines, which promote cancer cell growth, invasion, metastasis, drug resistance and dryness through paracrine effects. On the other hand, CAFs inhibit T cell activation by promoting recruitment of immunosuppressive cells, differentiation of monocytes into M2-type macrophages, or inhibition of tumor antigen processing by dendritic cells, etc. [27-30] and reshaping the immune microenvironment. More importantly, some CAFs cells express molecules such as PD-L2 and FASL, which directly induce T cell death by binding to T cell surface receptors [31].

Cohen et al. [32] found that CAFs in breast cancer can drive tumor immunosuppression by secreting Chi3L1, and building a microenvironment that promotes the growth of breast cancer cells. It can be seen that CAFs are important mesenchymal cells involved in regulating the formation of TNBC immunosuppressive microenvironment [27]. However, CAFs are a highly heterogeneous cell population, and the interaction between CAFs and immune cells in tumor tissues and their Spatio-temporal dynamic changes have not been fully understood, so it is difficult to implement stratified diagnosis and treatment of patients based on microenvironment immune characteristics [33].

5.3 Cytotoxic T Lymphocyte-associated Antigen 4(CTLA4) Therapy

CTLA-4 is a leukocyte differentiation antigen that is homologous to CD28. Similarly, PD-1 is also a homologous molecule of CD28. Therefore, PD-1 and CTLA-4 are both CD28-dependent T-cell co-inhibitory receptors [34] and participate in the negative regulation of immune response [35]. After T cells are heavily activated, CTLA-4 downregulates T cell function through up-regulated expression on the cell membrane, both by competing with CD28 for its ligand B7 to prevent co-stimulation and by inducing T cell cycle arrest [36]. In addition, CTLA-4 binds to CD80 and CD86 on dendritic cells to block T-cell-mediated immune responses. In 2011, the US FDA approved Ipilimumab, an anti-CTLA-4 antibody, for the treatment of metastatic melanoma. The anti-tumor mechanism of CTLA-4 antibody is to induce anti-tumor immunity by blocking fork-head/wing-shaped spiral transcription factor 3+(FOXP3+) regulatory T cells in the TME pathway to amplify T cells and enhance tumor cell rejection [37]. FOXP3+ plays a key role in tumor inhibition, and CD4+ FOXP3-T cells are important anti-tumor immune cells. Increasing the number of CD4+ FOXP3-T cells in tumor tissues can improve the efficacy of anti-PD-1 / anti-CTLA-4 combined therapy. Meanwhile, blocking both PD-1 and CTLA4 can activate both CD4+Foxp3-T cells and CD8+T cells [38].

5.4 Nano Drug Immunotherapy

Due to the immunosuppressive microenvironment of TNBC, some immune cells or cytokines injected through veins cannot successfully reach the tumor site, which leads to the remarkable effect of immunotherapy in hematologic tumors, but it is still unable to overcome solid tumors [39]. With the development of materials science and nanotechnology, nanomaterials are expected to provide new ideas for improving the effectiveness of immunotherapy. Because of their unique EPR effect, nanomaterials can enhance the drug enrichment at the tumor site, thus improving the therapeutic effect [40].

Macrophages are the main components of tumor tissues, and most tumor-associated macrophages (TAMs) are of the M2 type. This phenotype contributes to tumor growth and metastasis and causes drug resistance. The transformation of M2 type to M1 type by programming is considered to be an effective cancer treatment strategy [41,42]. Daldrup et al. [43-45] recently verified this concept by using iron oxide nanoparticles. The study used FDA-approved nano-sized ferrioxide, a system with no direct toxicity to several cancer and non-cancer lines, with concentrations up to 3 mg ml-1. Notably, only when co-cultured with macrophages did iron oxide nanoparticles cause a significant decrease in the viability of MMTV-PyMt-derived cancer cells, along with an 11- and 16-fold increase in hydrogen peroxide and hydroxyl number, respectively. These results suggest that in the presence of iron oxide nanoparticles, polarization into M1-type macrophages mediates the killing of cancer cells.

Studies have demonstrated that nano drugs are associated with cell autophagy, Li, etc., proof that doxorubicin-polyglycerol-nanometer diamond composite material by activating glioma cell autophagy, can stimulate the immunogenicity of the cells, the discovery of how nanotechnology used in the treatment of tumor immune microenvironment provides a new train of thought [46].
6 Conclusion and prospect

TME is varied, complex, and generally presents an immunosuppressive microenvironment. After entering TME, immune cells will produce a series of metabolic changes in response to this microenvironment, which is often characterized by immunosuppression and promotion of tumor occurrence and development. TME provides suitable conditions for tumor cells to colonize and interact with surrounding immune cells, fibroblasts, endothelial cells and other cells, while the interaction between tumor cells and other cells in TME can cause changes in TME and promote tumor invasive growth, neovascularization and metastasis of target organs. Due to the heterogeneity of breast cancer, it is necessary to understand the complex relationship between tumor cells and TME, and explore the mechanism of tumor development and guide subsequent treatment through the interaction between tumor cells and TME. TNBC has a unique TME, and the heterogeneity of TME is also related to the subtype of TNBC. Targeted TME therapy based on molecular typing will contribute to the realization of "precision medicine".

References


