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Immune Cell Infiltration Characteristics in the Tumor Microenvironment of Triple-Negative Breast Cancer and Their Prognostic Value

Yun Liu*

The Sixth Medical Center of the PLA General Hospital, Beijing 100000, China

***Correspondence to:** Yun Liu, The Sixth Medical Center of the PLA General Hospital, Beijing 100000, China, E-mail: cloudy2602@163.com

Abstract: Triple-negative breast cancer (TNBC) is characterized by the absence of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) expression, rendering endocrine therapy and anti-HER2 targeted therapy ineffective. As a result, therapeutic options for TNBC are limited, and the prognosis remains poor. In recent years, with the successful application of immunotherapy in various solid tumors, TNBC—recognized as the most immunogenic subtype of breast cancer—has attracted increasing attention, particularly regarding the immune cell infiltration patterns within its Tumor Microenvironment (TME). This review systematically summarizes the composition, functional states, spatial distribution, and interaction networks of key immune cell populations in the TNBC TME, including tumor-infiltrating lymphocytes (TILs), myeloid-derived suppressor cells (MDSCs), tumor-associated macrophages (TAMs), and regulatory T cells (Tregs). Furthermore, it comprehensively discusses the associations between these immune infiltration characteristics and clinicopathological features, therapeutic responses, and long-term survival outcomes of patients. This review aims to provide a theoretical basis and novel insights for the development of precision immunotherapy strategies in TNBC.

Keywords: Triple-negative breast cancer; tumor microenvironment; immune cell infiltration; tumor-infiltrating lymphocytes; prognosis; immunotherapy

Introduction

Breast cancer is one of the most common malignant tumors in women and is characterized by high heterogeneity. Based on molecular classification, breast cancer can be divided into four major subtypes, among which triple-negative breast cancer (TNBC) accounts for approximately 10%–20%. Due to the lack of ER, PR, and HER2 expression, TNBC patients do not benefit from endocrine therapy or anti-HER2 targeted therapy, and chemotherapy remains the first-line treatment. However, TNBC is highly aggressive, prone to recurrence and metastasis, and associated with poor survival outcomes, highlighting an urgent need for novel

therapeutic strategies in clinical practice. The tumor microenvironment (TME) plays a critical role in tumor initiation, progression, and treatment response. TNBC exhibits an immunologically active TME, characterized by a relatively high tumor mutational burden and neoantigen load, which facilitates the recruitment and activation of immune cells and contributes to the formation of so-called "hot tumors." In recent years, immune checkpoint inhibitors have achieved significant breakthroughs in the treatment of TNBC. For example, PD-L1 inhibitors in combination with chemotherapy have been approved for the treatment of specific patients with advanced TNBC, further driving in-depth research into immune cell infiltration patterns within the TNBC TME. A comprehensive understanding of the immune landscape of TNBC is of great significance for identifying patients who are most likely to benefit from immunotherapy and for optimizing therapeutic strategies. Therefore, this review aims to systematically summarize the immune cell infiltration characteristics of the TNBC TME and to elucidate their value in prognostic evaluation.

1. Overview of the Tumor Microenvironment in Triple-Negative Breast Cancer

The TME of TNBC is a dynamic and highly heterogeneous system. In addition to malignant epithelial cells, the TNBC TME contains a rich variety of non-tumor components, which mainly include the following elements.

(1) Immune cells: Immune cells represent the most prominent component of the TME and include both the adaptive and innate immune systems. Adaptive immune cells mainly consist of T lymphocytes and B lymphocytes, while innate immune cells include macrophages, dendritic cells (DCs), natural killer (NK) cells, neutrophils, and myeloid-derived suppressor cells (MDSCs), among others [1].

(2) Stromal cells: These are primarily represented by cancer-associated fibroblasts (CAFs), which support tumor growth and immune evasion through the secretion of cytokines and chemokines, as well as through remodeling of the extracellular matrix.

(3) Vascular endothelial cells: These cells form the tumor vascular network, which not only supplies nutrients and oxygen to tumor tissues but also serves as a critical route for immune cell trafficking into and out of the TME.

(4) Extracellular matrix (ECM): Composed mainly of collagen, fibronectin, and other structural proteins, the ECM provides both physical scaffolding and biochemical signals that regulate immune cell migration, localization, and functional activity.

In TNBC, high genomic instability leads to the generation of a large number of neoantigens. These neoantigens are captured and processed by antigen-presenting cells, such as DCs, and subsequently presented to T cells, thereby initiating antitumor immune responses. However, tumor cells simultaneously evolve multiple mechanisms to suppress these immune responses, resulting in a dynamic interplay between pro-inflammatory and immunosuppressive forces within the TME. The balance or imbalance of immune cell composition and function ultimately determines tumor progression and has a direct impact on patient prognosis.

2. Major Immune Cell Infiltration Characteristics in the TNBC Tumor Microenvironment

2.1 Tumor-Infiltrating Lymphocytes (TILs)

TILs are the most extensively studied immune cell population within the TME and show the clearest association with clinical prognosis. TILs mainly include $CD8^+$ cytotoxic T lymphocytes (CTLs), $CD4^+$ helper T cells (Th cells), and regulatory T cells (Tregs).

2.1.1 $CD8^+$ T Cells

As the primary effector cells of antitumor immunity, $CD8^+$ CTLs are capable of recognizing and directly killing tumor cells that express tumor-associated antigens. A large body of evidence has demonstrated that, in TNBC, the abundance of stromal tumor-infiltrating lymphocytes (sTILs)—particularly the level of $CD8^+$ T cell infiltration—is significantly and positively correlated with higher rates of pathological complete response (pCR), longer disease-free survival (DFS), and improved overall survival (OS). To standardize evaluation, the International TILs Working Group has established consensus guidelines for TILs assessment and recommends the routine inclusion of sTIL percentage evaluation in pathological reports of TNBC. This metric is increasingly recognized as a potential prognostic and predictive biomarker.

2.1.2 $CD4^+$ T Cells

$CD4^+$ T cells exhibit diverse functional phenotypes. Among them, the Th1 subset exerts antitumor effects by secreting cytokines such as interferon-γ (IFN-γ), thereby activating macrophages and $CD8^+$ T cells. In contrast, the roles of Th2 and Th17 subsets are more complex and context-dependent, potentially exerting either tumor-promoting or tumor-suppressive effects under different conditions. Overall, infiltration of Th1-polarized $CD4^+$ T cells in TNBC is generally associated with favorable clinical outcomes.

2.1.3 B Lymphocytes

Although historically less studied, accumulating evidence suggests that B lymphocytes within the TME—and the tertiary lymphoid structures (TLS) they form—play an important antitumor role in TNBC. TLS are ectopic lymph node–like structures composed of distinct T-cell zones and B-cell follicles, serving as local hubs for antigen presentation and adaptive immune responses [2]. The presence of TLS in TNBC is often associated with improved prognosis and may also predict enhanced responsiveness to immunotherapy.

2.2 Myeloid-Derived Suppressor Cells (Myeloid-Derived Suppressor Cells, MDSCs)

Myeloid-derived suppressor cells (MDSCs) are a heterogeneous population of immature myeloid cells that expand under pathological conditions such as cancer and chronic inflammation and exhibit potent immunosuppressive activity. MDSCs suppress T-cell activation and proliferation primarily through the production of reactive oxygen species (ROS), nitric oxide (NO), and arginase-1 (ARG1), while simultaneously promoting the expansion of regulatory T cells (Tregs). In patients with TNBC, elevated levels of MDSCs are commonly observed in both peripheral blood and the tumor microenvironment. Increased MDSC abundance is positively correlated with advanced tumor stage and metastatic risk, and negatively correlated with patient survival, identifying MDSCs as an important indicator of poor prognosis.

2.3 Tumor-Associated Macrophages (TAMs)

Macrophages are among the most abundant myeloid cell populations within the TME. Based on their polarization status, they are broadly classified into classically activated M1 macrophages, which exhibit antitumor activity, and alternatively activated M2 macrophages, which promote tumor progression. In the TNBC TME, TAMs predominantly display an M2-like phenotype, characterized by high expression of markers such as CD163 and CD206. M2-polarized TAMs suppress T-cell function through the secretion of immunosuppressive cytokines, including interleukin-10 (IL-10) and transforming growth factor-β (TGF-β). In addition, they promote angiogenesis, tumor growth, invasion, and metastasis by producing vascular endothelial growth factor (VEGF), epidermal growth factor (EGF), and other pro-tumorigenic mediators. Multiple studies have demonstrated that high infiltration of M2-like TAMs in TNBC is closely associated with shorter disease-free survival (DFS) and overall survival (OS).

2.4 Regulatory T Cells (Regulatory T Cells, Tregs)

Regulatory T cells (Tregs), typically defined by the phenotype $CD4^+CD25^+FoxP3^+$, play a central role in maintaining immune tolerance but paradoxically facilitate immune evasion in the context of cancer. Tregs suppress effector T-cell responses through both cell contact–dependent mechanisms, such as cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4), and contact-independent mechanisms, including the secretion of immunosuppressive cytokines such as IL-10 and TGF-β. In TNBC, the prognostic significance of Treg infiltration remains complex and somewhat controversial. On one hand, high levels of Tregs are generally associated with an immunosuppressive microenvironment and unfavorable clinical outcomes. On the other hand, because Treg infiltration often coincides with increased overall T-cell infiltration, some studies have reported a positive association between Tregs and favorable prognosis. This apparent contradiction may reflect the broader immune context of the TME, suggesting that evaluation of Tregs alone may be insufficient to determine their net biological effect. Comprehensive assessment in combination with other immune cell populations is therefore required.

2.5 Other Immune Cell Populations

(1) Natural killer (NK) cells: As a key component of the innate immune system, NK cells can directly recognize and eliminate tumor cells that lack major histocompatibility complex class I (MHC-I) molecules. In TNBC, NK cell activity is frequently attenuated

by immunosuppressive signals within the TME. Consequently, the functional status of NK cells, rather than their absolute abundance, may represent a more meaningful prognostic indicator.

(2) Neutrophils: Tumor-associated neutrophils (TANs) also exhibit functional heterogeneity and are commonly categorized into antitumor N1 and protumor N2 phenotypes. In TNBC, N2-polarized TANs tend to predominate. These cells facilitate tumor invasion through the release of matrix metalloproteinases (MMPs) and contribute to immune suppression by inhibiting T-cell function.

3. Spatial Heterogeneity and Interactions of Immune Cell Infiltration

Immune cells within the TME are not randomly distributed; rather, their spatial localization is critical for functional activity. For example, intratumoral $CD8^+$ T cells located within the tumor core are more capable of directly contacting and eliminating tumor cells than $CD8^+$ T cells restricted to the stromal compartment, and therefore exhibit greater prognostic significance. In addition, the spatial proximity among different immune cell populations reflects their functional interactions. Emerging technologies such as multiplex immunohistochemistry (mIHC) and spatial transcriptomics have revealed distinct immune spatial phenotypes in TNBC. Patients with "immune-excluded" or "immune-desert" phenotypes show significantly worse clinical outcomes compared with those exhibiting an "immune-inflamed" phenotype [3]. Immune cells within the TME form a complex regulatory network. For instance, M2-polarized TAMs can recruit and activate regulatory T cells (Tregs), which in turn further promote macrophage polarization toward the M2 phenotype. Myeloid-derived suppressor cells (MDSCs) function as a central immunosuppressive hub, broadly inhibiting the activity of T cells and natural killer (NK) cells while facilitating the expansion of TAMs and Tregs. This cooperative immunosuppressive network represents a core mechanism of immune evasion in TNBC and constitutes a key target for the rational design of combination immunotherapy strategies.

4. Prognostic Value of Immune Infiltration Characteristics

A substantial body of clinical evidence has established the strong prognostic value of immune infiltration characteristics in TNBC.

(1) TILs as independent prognostic factors: Multiple large retrospective and prospective studies, including FinHER and GeparSixto, have consistently demonstrated that for every 10% increase in stromal tumor-infiltrating lymphocytes (sTILs) in preoperative or postoperative tumor specimens, the risk of disease recurrence and death is significantly reduced. This association is particularly pronounced in the neoadjuvant chemotherapy setting, where high TIL levels serve as a powerful predictor of pathological complete response (pCR). Notably, pCR itself is a well-established surrogate marker for favorable long-term survival.

(2) Immune gene expression signatures: Beyond morphological assessment, immune-related gene expression signatures derived from RNA sequencing or NanoString platforms—such as interferon-γ (IFN-γ) signaling pathways and cytolytic activity–related genes—can effectively quantify immune activation within the TME. These molecular signatures exhibit prognostic value comparable to that of TILs and may provide more refined functional insights into antitumor immune responses [4].

(3) Integrated immune scoring systems: To more comprehensively characterize the immune status of the TME, increasing efforts have been made to integrate multiple immune parameters. Composite indicators, such as the $CD8^+$/Treg ratio and the $CD8^+$/$CD163^+$ TAM ratio, have been proposed as measures of immune balance. These ratios often demonstrate superior prognostic discrimination compared with the absolute abundance of individual immune cell populations.

Importantly, the prognostic impact of immune infiltration may vary depending on treatment modality. In patients receiving immunotherapy, baseline immune features of the TME—such as programmed death-ligand 1 (PD-L1) expression, tumor mutational burden (TMB), and TIL levels—are critical predictors of therapeutic response. Meanwhile, even in patients treated exclusively with chemotherapy, high immune infiltration remains associated with improved outcomes. This observation underscores the fundamental role of endogenous antitumor immunity in restraining TNBC progression.

Conclusion

The TME of TNBC is distinguished from other breast cancer subtypes by its unique immunologically active characteristics. Among the various immune components, the abundance and functional status of effector immune cells—most notably TILs, particularly $CD8^+$ T cells—represent key determinants of favorable clinical outcomes. In contrast, the expansion of immunosuppressive populations, including MDSCs, M2-polarized TAMs, and regulatory T cells, constitutes a major barrier to effective antitumor immunity and is closely associated with poor prognosis. The composition, spatial distribution, and complex interaction networks of these immune cell populations collectively shape the immune landscape of TNBC. A deeper and more comprehensive understanding of this landscape not only enables more precise prognostic stratification of patients but also serves as a critical foundation for guiding immunotherapeutic strategies, developing novel combination therapies, and ultimately improving survival outcomes in TNBC. With continued technological advances and ongoing research efforts, precision medicine approaches based on TME immune characteristics are expected to play an increasingly important role in the clinical management of TNBC.

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