Transactions on Materials, Biotechnology and Life Sciences
ISSN: 2960-1932, eISSN: 2960-2319 | Volume 8
MMTCS 2025

Applications of the Tumor Microenvironment in Breast Cancer Treatment

Siyu Huo *

Department of Chemistry, College of Science, China Agricultural University, Beijing, 100193, China

* Corresponding Author Email: 2024310060302@cau.edu.cn

Abstract. Research on the tumor microenvironment (TME) in breast cancer (BC) has witnessed substantial advancements in recent decades, with a growing emphasis on elucidating its key cellular and molecular components as well as their dual roles in either promoting or suppressing tumor progression. These investigations have laid the foundation for innovative therapeutic strategies targeting TME dynamics. Clinically, the heterogeneity of TME has already been exploited for diagnostic purposes, while an expanding array of immunotherapies and molecularly targeted agents are being incorporated into treatment regimens for specific BC subtypes. This review systematically examines the structural and functional complexity of TME, while providing a comprehensive synthesis of its current applications in BC immunotherapy and precision medicine. These discussions are anticipated to offer novel conceptual frameworks for future research, potentially guiding the development of next-generation treatments that exploit the tumor-modulating properties of TME components through more sophisticated mechanistic approaches.

Keywords: Tumor microenvironment; immunotherapy; breast cancer; targeted therapy.

1. Introduction

Cancer is one of the leading causes of death worldwide and a significant barrier to extending human longevity. Among all types of cancer, BC ranks highly in terms of the number of cases and is currently one of the most common cancers worldwide [1]. It is also a significant cause of cancer-related deaths among women. In 2020 alone, it was estimated that there were 2.3 million new cases, which accounted for 11.7% of all cancer diagnoses. [2]. Irregular and heritable genetic mutations in germ cells or somatic cells are significant causes of malignant tumors. BC also arises from the accumulation of specific genetic mutations caused by both genetic and environmental factors. It is estimated that about 10% of female BC patients have a family history of the disease [3]. According to gene expression data, BC can be categorized into five distinct subtypes: human epidermal receptor 2 (HER2) -enriched, Luminal A, Luminal B, Basal-like, and Claudin-low [4]. The clinical management and prognosis of BC are contingent upon the subtype, which is determined by the expression of HER2 and hormone receptors, as evaluated through immunohistochemistry, along with the disease stage [4]. Advanced-stage BC is almost invariably fatal, necessitating continuous therapeutic intervention for patients.

At present, BC poses a serious threat to human health and quality of life, its clinical treatment methods, meanwhile, are an extremely popular research area. However, the most widely used therapy for BC is still predominantly chemotherapy, which employs drugs characterized by strong cytotoxicity and weak targeting, leading to significant side effects during treatment and considerable suffering for patients. Therefore, exploring the mechanisms of cancer formation and progression, and subsequently seeking new and more efficient therapies for BC, is of paramount importance to researchers.

In the process of cancer development, the continuous adaptation of the tumor microenvironment (TME) is essential for promoting tumor growth. TME constitutes the milieu surrounding a tumor, encompassing immune cells, the extracellular matrix, adjacent vasculature, and other cellular entities. As tumorigenesis progresses, neoplastic cells exhibit surface protein molecules that inhibit immune cells capable of tumoricidal activity, while concurrently recruiting additional cells to collectively suppress immune responses. These cellular components collectively form TME. The induction of

tumor cell proliferation, angiogenesis, immune system suppression, and evasion of immune surveillance are all closely linked to the tumor microenvironment [5]. TME itself is highly complex and heterogeneous, and the cancer cells within it can undergo a reprogramming process due to hypoxia caused by rapid proliferation tumor cells and the surrounding TME cells continuously adapt to new conditions and promote the growth of the tumor. The cells constituting TME play a pivotal role in shaping the pathology of the disease [6]. In practice, these cells not only have the capacity to facilitate the progression of the disease but, conversely, they may also suppress tumor growth through adaptive immunity. This is most notably reflected in epidemiological data, which indicates that immunocompromised individuals exhibit a significantly higher risk of developing cancer and experience greater cancer-related mortality [7]. Such insights provide a rationale for the development of novel therapeutic strategies for BC, which involve modulating TME to effectuate beneficial alterations in its composition, thereby enhancing adaptive immune responses and bolstering resistance against tumorigenesis.

Recently, high-resolution technologies have revealed that variations in patient treatment progression and outcomes are closely associated with extensive heterogeneity within and across subtypes in the BC TME. A critical point is that there are not only quantitative but also qualitative differences among lymphocyte, myeloid, and fibroblast populations within TME, leading to distinct disease pathologies [8]. In fact, within each immune cell and another stromal cell type in TME, there exist discrete cell populations capable of promoting, suppressing, or driving anti-tumor immune responses [8]. Therefore, targeted and differentiated research into the compositional differences of TME among BC subtypes, as well as between BC and other cancer types, is essential for developing more effective therapeutic strategies.

This review commences with the delineation of the specific composition of the tumor microenvironment (TME) in BC. Special emphasis is placed on the immune cells within the TME and how they expound on the mechanisms, processes, and influencing factors related to their pro - tumorigenic and anti - tumorigenic roles. Additionally, it discusses how TME evolves as the disease progresses, the dynamic interactions between the immune system and the tumor during this process, and how these mechanisms can be utilized for clinical therapeutic applications. It also examines the current state of using TME components for the development of BC immunotherapies and summarizes the applications of TME in BC diagnosis and clinical treatment. Finally, it addresses the latest advancements in using TME components for BC immunotherapy and the challenges faced by related research efforts.

2. Mechanisms of Cancer Promotion and Suppression Involving Key Components in the Tumor Microenvironment

TME constitutes a complex ecosystem. The composition and functional state of TME exhibits significant variations depending on the tumor type, intrinsic characteristics, disease stage, and patient-specific factors. Therefore, elucidating the key components of TME, along with their intricate interactions in disease progression and their dual roles in promoting or suppressing tumorigenesis, is critical for the rational development of effective anticancer therapeutics.

2.1. Key Components of the Tumor Microenvironment

The immune cells within TME primarily include CD8+ T-cells, CD4+ T-cells, regulatory B cells (Bregs), tumor-associated macrophages (TAMs), and natural killer (NK) cells. CD8+ T-cells, named for their expression of the CD8 protein molecule, are typically potent tumor-killing cells, also known as CD8 cytotoxic T-cells. They recognize the major histocompatibility complex (MHC) and peptide-bound protein molecules on the tumor surface through protein molecules on the T-cell surface. The binding of these two protein molecules facilitates the secretion of cytokines by CD8+ T-cells, leading to the disintegration and apoptosis of tumor cells. Another type of T-cell, CD4+ T-cells, are generally

helper T-cells. They assist other immune cells, particularly CD8+ T-cells, in recognizing MHC and peptide-bound protein molecules by secreting cytokines, thereby involving them in tumor regulation.

Regulatory B cells are the primary mediators of humoral immunity, capable of secreting antibodies and participating in humoral immune responses. Their anti-tumor effects are also exerted through antibody-dependent cellular cytotoxicity. In addition to antibody dependency, they can also activate the complement pathway, which similarly exerts anti-tumor effects. B cells in TME are mainly found in structures associated with stimulated lymphoid tumors, where they can promote T-cell activation and the presentation of certain antigens to exert anti-tumor effects.

In addition to T-cells and B cells, there are various other types of immune cells, such as macrophages, which are highly plastic immune cell populations capable of directly engulfing cancer cells, and NK cells, which are innate lymphoid cells and powerful anti-cancer cells capable of recognizing and killing cells lacking MHC class I expression. Another important component of TME is cancer-associated fibroblasts (CAFs), which serve as the scaffold in TME. They not only secrete growth factors to promote tumor growth but also secrete components of the extracellular matrix (ECM), supporting the development of tumor cells within the microenvironment. The ECM also plays a significant role in TME, acting not only as a physical scaffold for cells but also dynamically regulating cell behavior, including migration, survival, and response to treatment. Lastly, vascular cells are another cell type that cannot be overlooked. Tumor vasculature is typically disorganized and dysfunctional, increasing interstitial pressure within the tumor and thereby limiting the effective delivery of therapeutic agents.

In-depth characterization of TME reveals the complex interplay between immune cells and stromal cells, which can both promote and inhibit anti-tumor immunity. Compared to most tumor types, triple-negative breast cancer (TNBC) and HER2-overexpressing subtypes often have a richer population of tumor-infiltrating lymphocytes (TILs). Due to differences in the quantity and quality of immune cell populations, the diversity of TME is evident in each BC subtype, leading to the dual role of different elements of the immune TME in both limiting and promoting tumor growth [9].

2.2. Tumor-Promoting Mechanisms of the Tumor Microenvironment

Tumor cells, as mutated cancer cells derived from somatic cells, often express specific protein molecules on their surface. These protein molecules are recognized by the immune system as normal somatic cells, thereby enabling tumor cells to evade immune surveillance, suppress immune responses, and promote tumor growth. Common immune checkpoint proteins exploited by tumors to mimic normal cells include PD-1 and CTLA-4, which play critical roles in helping the immune system distinguish between normal and abnormal cells. Tumor cells frequently exploit this mechanism to escape detection by immune cells.

As the tumor progresses, immune cells gradually become functionally exhausted. T-cells are the first to be depleted, followed by the growth of the extracellular matrix and the formation of blood vessels within the tumor, which supply oxygen and nutrients. The cellular composition of the surrounding TME undergoes gradual changes, with an increase in the number of Tregs. These Tregs normally function to suppress the immune system's attack on normal somatic cells during excessive immune responses. However, their excessive accumulation also inhibits the immune system's ability to target tumor cells, further facilitating tumor proliferation.

During tumor development, the surrounding blood vessels become more numerous and extensive. Subsequently, tumor stem cells may enter the bloodstream or lymphatic system, spreading to other parts of the body through the circulatory system, a process known as tumor metastasis. In these new locations, a new TME forms, repeating the cycle from initial establishment to the successful colonization of the tumor.

2.3. Tumor-Suppressive Mechanisms of the Tumor Microenvironment

In addition to the intrinsic tumor-suppressing mechanisms of T-cells, NK cells, and macrophages, which recognize and eliminate tumor cells, dendritic cells (DCs) within TME serve as antigen-presenting cell populations. Through interactions with tumor cells, DCs capture and transmit tumor antigen information, thereby amplifying tumor antigen signals. This process further activates and enhances immune cell responses, exerting potent anti-tumor effects. Moreover, CAFs also participate in tumor-suppressing mechanisms within TME. For instance, α-SMA+ myofibroblast populations can inhibit the function of regulatory Tregs while maintaining the anti-tumor activity of CD8+ T-cells, thereby enhancing the immune system's ability to target and destroy tumors [10].

Furthermore, other components of TME contribute to anti-tumor mechanisms. For example, tumor-infiltrating B cells (TIBs) can, in certain contexts, inhibit tumor growth by producing anti-tumor antibodies or activating T-cells. Similarly, tumor-associated neutrophils (TANs) can differentiate into an anti-tumor phenotype (N1 type) under specific conditions, suppressing tumor progression by releasing cytotoxic substances and promoting T-cell infiltration [11]. On the other hand, ECM components within TME, such as collagen and fibronectin, can influence anti-tumor immune responses by modulating the migration and function of immune cells. However, the dynamic balance of TME is highly complex, and in some cases, these components may be co-opted by tumor cells to foster a pro-tumorigenic microenvironment. Therefore, in-depth research into the anti-tumor mechanisms within TME is crucial for developing more effective cancer treatment strategies.

3. The Application of Tumor Microenvironment in Clinical Diagnosis and Treatment

The complex composition of the TME and its dual tumor-promoting and tumor-suppressing mechanisms have gradually found applications in clinical practice. Notably, the marked heterogeneity of the TME and its dynamic interactions with the immune system represent highly promising research directions for further exploration in the clinical diagnosis and treatment of BC.

3.1. The Application of Tumor Microenvironment in Breast Cancer Diagnosis

The components of TME exhibit significant heterogeneity across different types of cancer and BC subtypes, a characteristic that underscores the broad diagnostic utility of TME in BC. For instance, the adaptive arm of the immune system is represented by TILs, which are primarily made up of CD3+T cells. Their existence indicates an antitumor host immunological response. One of TME's best-characterized components, TILs is particularly pertinent to clinical outcomes [12]. The sole biomarker linked to a better prognosis in TNBC, as well as a better response to chemotherapy and ICB, is TIL number [13]. In clinical diagnostics, the assessment of TILs is undergoing international standardization and is increasingly being applied to evaluate disease status, prognosis, and recurrence risk in patients with TNBC and HER2-positive BC. Furthermore, various T-cell subsets serve as important biomarkers in BC diagnosis. Among BC subtypes, TNBC exhibits the highest abundance of TILs, which is thought to be associated with its relatively high tumor mutational burden (TMB), frequent TP53 mutations, and genomic instability [14]. In studies of primary breast tumors, researchers have observed significant infiltration of CD3+ T-cells, particularly in HER2-enriched, and TNBC subtypes. Overall, higher densities of CD8+ and CD4+ TILs correlate with increased effector T-cell activity, suggesting that tumors with elevated TIL infiltration may exhibit improved clinical outcomes. Consequently, variations in T-cell distribution across cancer subtypes are often utilized to identify tumors likely to respond to immunotherapy [15].

3.2. The Application of Tumor Microenvironment in Clinical Breast Cancer Treatment

TME’s complex composition and dual mechanisms of promoting and suppressing cancer are often utilized by researchers as a focal point for developing novel BC therapies. For instance, given that the immune homeostasis function of regulatory T-cells may sometimes assist tumor cells in evading recognition by cytotoxic immune cells such as CD8+ T-cells and NK cells, endogenous NK cells can

be mobilized, or existing NK cells can be genetically modified and reinfused into patients to enhance their cytotoxic activity, thereby further activating the immune system.

Currently, numerous research teams in clinical settings have developed therapies and drugs targeting the pro-tumorigenic mechanisms of TME, primarily focusing on immune checkpoint inhibitors. These therapies mainly target the ligand-receptor interactions between proteins expressed by antigen-presenting cells and T-cells, which have been relatively well-studied. Additionally, some teams concentrate on targeted therapies for BC TME. For example, based on the distinct molecular profile of TNBC—including alterations in the cell cycle, PI3K/AKT/mTOR and/or phosphatase and tensin homolog (PTEN) pathways, amplification of growth factor receptors, RAS/mitogen-activated protein kinase (MAPK) pathway modifications, and DNA repair defects—specific drugs such as anti-angiogenic agents, cell cycle inhibitors, and MAPK or PI3K pathway inhibitors can be selected to address these abnormalities [16].

4. Current Advances in Breast Cancer Tumor Microenvironment Research and Challenges in Clinical Application

Over the years, substantial efforts have been devoted to investigating the components of TME and their specific associations with BC progression, as well as the underlying mechanisms of tumor promotion. While significant advances have been made in clinical applications, several challenges remain in this field.

4.1. Current Research Advances in the Tumor Microenvironment of Breast Cancer and Its Applications

For a considerable duration, significant efforts have been devoted to investigating TME's specific associations with BC development. It can be asserted that the continuous interplay between tumor cells and TME plays a decisive role in tumor initiation, progression, metastasis, and treatment response. Consequently, researchers have prioritized targeting TME in drug development and clinical trials to enhance therapeutic efficacy.

Simultaneously, investigations into TME components have led to the exploration of novel technologies and methodologies aimed at deciphering the tumor microenvironment more effectively. These efforts seek to develop strategies for intervening in TME's pro-tumorigenic mechanisms and maximizing therapeutic benefits. Overall, current research on BC treatment primarily focuses on immunotherapy and targeted therapy. Immunotherapy can be broadly categorized into three types: immune checkpoint blockade, cell therapy, and anticancer vaccines.

Immune checkpoints are closely associated with T-cell activation and tolerance. The PD-1 (programmed cell death protein-1)/PD-L1 (programmed death-ligand 1) axis and cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) serve as key inhibitory signals that suppress T-cell immune responses. As a result, extensive research is dedicated to developing immune checkpoint inhibitors, including anti-PD-1, anti-PD-L1, and anti-CTLA-4 monoclonal antibodies, with additional candidates still under investigation. Among these, anti-PD-1 antibodies such as cemiplimab, pembrolizumab, and nivolumab; anti-PD-L1 antibodies such as nivolumab, atezolizumab, and durvalumab; and anti-CTLA-4 agents like tremelimumab and ipilimumab have demonstrated therapeutic potential and have been approved for clinical use in treating various malignancies [18].

Another category, cell therapy, primarily includes CAR-T cell therapy and NK cell therapy, which functions by enhancing the activity of immune cells to directly target cancer cells. Anticancer vaccines represent another prominent therapeutic approach, operating by training the immune system to recognize cancer cells, thereby enabling a faster and more robust immune response in the event of recurrence. Based on delivery methods, cancer vaccines can be classified into three types: DNA-based tumor vaccines, RNA-based tumor vaccines, and protein/peptide-based tumor vaccines.

DNA vaccines are prepared by encoding tumor antigens into DNA, which is then administered via injection. Dendritic cells (DCs) subsequently uptake this DNA, facilitating intracellular transcription and translation, followed by antigen presentation to T-cells. In contrast, RNA tumor vaccines enable more rapid protein expression. Delivered via lipid nanoparticles or similar carriers, they directly enter the antigen presentation process, thereby improving antigen delivery efficiency. Distinct from these two approaches, protein/peptide-based tumor vaccines utilize longer peptides compared to traditional short peptides, allowing for enhanced processing and presentation by dendritic cells, which in turn induces a stronger immune response. Following processing in dendritic cells, these long peptides are more effectively presented on MHC molecules, leading to superior activation of CD8+ T-cells.

In contrast to immunotherapy, targeted therapy employs drugs designed to inhibit specific proteins that support the growth, dissemination, and proliferation of BC cells [19]. Several targeted drugs have already been introduced into clinical practice. For instance, the mTOR inhibitor zortress (42-O-(2-hydroxyethyl) rapamycin) has been approved for the treatment of advanced or metastatic aromatase inhibitor-resistant ER+ BC [20].

4.2. Challenges in Clinical Application

Although significant progress has been made in the study of TME in BC, numerous challenges persist in clinical applications, with several critical issues remaining unresolved. For instance, targeted therapeutic agents exhibit a dual effect: while they are designed to activate and enhance the immune system's response against cancer cells by leveraging the body's inherent immune mechanisms to eliminate malignancies, they may also lead to excessive immune activation, resulting in attacks on healthy somatic cells. This can trigger autoimmune reactions, such as inflammation or even neurotoxicity. Such overactivation of the immune system represents one of the adverse effects associated with targeted immunotherapies.

Additionally, due to high molecular heterogeneity, targeted therapies for TNBC are limited to a small number of common actionable targets. Moreover, treatments focusing on a single target are prone to drug resistance, which restricts their therapeutic efficacy. Consequently, combination therapies targeting multiple pathways have become the most prevalent strategy in clinical trials [21]. Some studies have also reported instances of pseudoprogression in patients following immunotherapy for TNBC. Pseudoprogression refers to an initial increase in tumor size followed by a subsequent reduction in tumor burden, which is associated with immune cell infiltration, edema, or necrosis induced by immunotherapy. Thus, the evaluation of immunotherapy efficacy requires further investigation [22].

Regarding BC vaccines, multiple challenges remain in current research. Clinical trials have observed that the immunity elicited by vaccination tends to diminish over time, likely due to insufficiently sustained antitumor immune stimulation, which fails to generate durable and potent anticancer effects [23]. Vaccine stimulation may even lead to reduced immunity against BC or induce immune tolerance in some patients. Therefore, sustaining the suppression of immune tolerance and effectively harnessing the patient's natural immune response remain key challenges in improving the efficacy of BC vaccines.

5. Conclusion

TME, as a critical factor influencing tumor progression, plays an indispensable role in the development and metastasis of BC. In BC-related research, TME has gradually emerged as one of the most prominent focal points. Numerous researchers have conducted in-depth investigations into the mechanisms by which its key components either promote or suppress cancer and the extended applications of these findings have already achieved tangible progress in clinical practice. Several newly developed therapies targeting TME have been implemented in actual treatment protocols.

The components of TME have been progressively elucidated. As the surrounding milieu of tumors, it encompasses immune cells, the ECM, adjacent vasculature, and other stromal cells. TME primarily

forms during tumorigenesis and progression, wherein the tumor surface expresses specific protein molecules that recruit other cells to collectively suppress immune activity. These cells collectively constitute TME. It can be posited that TME creates an exceptionally permissive condition for communication and interaction between cancer cells and their neighboring endothelial cells, immune cells, and fibroblasts. This facilitates the induction of TME components by cancer cells and their stromal counterparts to change conducive to further tumor progression, thereby increasing the likelihood of metastatic dissemination.

Within TME, immune cells primarily include CD8+ T-cells, CD4+ T-cells, regulatory Bregs, TAMs, and NK cells. These immune cells typically recognize and eliminate cancer cells by detecting tumor-specific proteins and engaging in intercellular signaling. However, cancer cells have evolved countermeasures, such as expressing surface proteins that mimic normal somatic cells, thereby evading immune surveillance and inducing functional exhaustion in immune cells. Beyond these immune effectors, DCs, as antigen-presenting cells, play a pivotal role in TME's operational dynamics in BC by transmitting tumor antigen information and amplifying associated signals.

Currently, these key components and mechanisms of TME are being progressively integrated into clinical diagnostics and therapeutics. In BC diagnosis, the quantity and compositional differences of TILs can be utilized to assess the clinical status of patients with TNBC and HER2-positive BC. Additionally, specific T-cell subsets may serve as biomarkers for diagnostic purposes.

In terms of treatment, current anti-cancer strategies derived from TME component and mechanism research primarily fall into two categories: immunotherapy and targeted therapy. Immunotherapy is further subdivided into three main approaches: immune checkpoint blockade, cell-based therapy, and cancer vaccines. Given the close relationship between immune checkpoints and T-cell activation/tolerance, immune checkpoint blockade strategies focus on developing inhibitors to disrupt tumor-derived immunosuppressive signals, such as immune checkpoint proteins and related antigens. Cell-based therapy predominantly involves engineering immune cells like CAR-T cells and NK cells to directly enhance their anti-tumor functionality against BC. Cancer vaccines operate by introducing tumor antigen preparations into the body, thereby training and activating the immune system's memory and responsiveness against malignant cells. In contrast to immunotherapy, targeted therapy employs drugs designed to specifically inhibit proteins critical for BC cell proliferation and survival. These targeted agents act on oncogenic drivers, thereby restricting tumor growth and dissemination.

This paper summarizes the principles and research advancements in utilizing the pro-tumorigenic and anti-tumor mechanisms of key immune components within TME for BC treatment, aiming to provide insights for future exploration of novel therapeutic approaches. Although several targeted drugs and cancer vaccines have been approved for clinical use, the challenges faced by immunotherapy and targeted therapy remain significant. For instance, the dual effects of targeted drugs may lead to immune-mediated damage to normal somatic cells, while cancer vaccines may inadvertently induce immune tolerance in patients. Therefore, with further research into the immune mechanisms within TME, more precise, effective, and personalized treatment strategies may soon emerge. To address the issue of insufficient long-term efficacy of cancer vaccines, future studies should focus on optimizing immunization dosage, administration routes, and the selection of immune boosters. Current research has demonstrated that booster vaccinations can sustain immunity and reduce the likelihood of recurrence in vaccinated populations. Additionally, future cancer vaccine formulations should be tailored to specific BC subtypes and their unique characteristics, potentially mitigating immune tolerance.In summary, developing novel BC therapies based on the components and mechanisms of TME represents a promising research direction. However, future clinical trials must account for patients' specific conditions and immune system functionality. Before more research findings can be translated into clinical practice, there remains substantial scope for further investigation in optimizing therapeutic efficacy and targeting, as well as in developing combination therapies.

References

[1] Wilkinson L, Gathani T. Understanding breast cancer as a global health concern. The British Journal of Radiology, 2022, 95 (1130): 20211033.

[2] Sung H, Ferlay J, Siegel RL, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA: A Cancer Journal for Clinicians, 2021, 71 (3): 209-249.

[3] Karim AM, Eun Kwon J, Ali T, et al. Triple-negative breast cancer: epidemiology, molecular mechanisms, and modern vaccine-based treatment strategies. Biochemical Pharmacology, 2023, 212: 115545.

[4] Perou CM, Sørlie T, Eisen MB, et al. Molecular portraits of human breast tumours. Nature, 2000, 406 (6797): 747-752.

[5] Hanahan D, Coussens LM. Accessories to the crime: functions of cells recruited to the tumor microenvironment. Cancer Cell, 2012, 21 (3): 309-322.

[6] Swanton C, Bernard E, Abbosh C, et al. Embracing cancer complexity: hallmarks of systemic disease. Cell, 2024, 187 (7): 1589-1616.

[7] Engels EA. Epidemiologic perspectives on immunosuppressed populations and the immunosurveillance and immunocontainment of cancer. American Journal of Transplantation, 2019, 19 (12): 3223-3232.

[8] Harris MA, Savas P, Virassamy B, et al. Towards targeting the breast cancer immune microenvironment. Nature Reviews Cancer, 2024, 24 (8): 554-577.

[9] Danenberg E, Bardwell H, Zanotelli VRT, et al. Breast tumor microenvironment structures are associated with genomic features and clinical outcome. Nature Genetics, 2022, 54 (5): 660-669.

[10] Kennel KB, Bozlar M, De Valk AF, et al. Cancer-associated fibroblasts in inflammation and antitumor immunity. Clinical Cancer Research, 2023, 29 (6): 1009-1016.

[11] Xiong S, Dong L, Cheng L. Neutrophils in cancer carcinogenesis and metastasis. Journal of Hematology & Oncology, 2021, 14 (1): 173.

[12] Salgado R, Denkert C, Campbell C, et al. Tumor-infiltrating lymphocytes and associations with pathological complete response and event-free survival in HER2-positive early-stage breast cancer treated with lapatinib and trastuzumab: a secondary analysis of the NeoALTTO trial. JAMA Oncology, 2015, 1 (4): 448-454.

[13] Loi S, Salgado R, Schmid P, et al. Association between biomarkers and clinical outcomes of pembrolizumab monotherapy in patients with metastatic triple-negative breast cancer: KEYNOTE-086 exploratory analysis. JCO Precision Oncology, 2023, 7: e2200317.

[14] Luen S, Virassamy B, Savas P, et al. The genomic landscape of breast cancer and its interaction with host immunity. Breast, 2016, 29: 241-250.

[15] Savas P, Virassamy B, Ye C, et al. Single-cell profiling of breast cancer T cells reveals a tissue-resident memory subset associated with improved prognosis. Nature Medicine, 2018, 24 (7): 986-993.

[16] Li L, Zhang F, Liu Z, et al. Immunotherapy for triple-negative breast cancer: combination strategies to improve outcome. Cancers, 2023, 15 (1): 321.

[17] Schütz F, Stefanovic S, Mayer L, et al. PD-1/PD-L1 pathway in breast cancer. Oncology Research and Treatment, 2017, 40 (5): 294-297.

[18] Debien V, De Caluwé A, Wang X, et al. Immunotherapy in breast cancer: an overview of current strategies and perspectives. npj Breast Cancer, 2023, 9(1): 7.

[19] Baudino TA. Targeted cancer therapy: the next generation of cancer treatment. Current Drug Discovery Technologies, 2015, 12 (1): 3-20.

[20] Ye F, Dewanjee S, Li Y, et al. Advancements in clinical aspects of targeted therapy and immunotherapy in breast cancer. Molecular Cancer, 2023, 22 (1): 105.

[21] Hu Y, Wang C, Liang H, et al. The treatment landscape of triple-negative breast cancer. Medical Oncology, 2024, 41 (10): 236.

[22] Emens LA, Cruz C, Eder JP, et al. Long-term clinical outcomes and biomarker analyses of atezolizumab therapy for patients with metastatic triple-negative breast cancer: a phase 1 study. JAMA Oncology, 2019, 5 (1): 74-82.

[23] Mittendorf EA, Clifton GT, Holmes JP, et al. Final report of the phase I/II clinical trial of the E75 (nelipepimut-S) vaccine with booster inoculations to prevent disease recurrence in high-risk breast cancer patients. Annals of Oncology, 2014, 25 (9): 1735-1742.