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REVIEW ARTICLE | OPEN ACCESS |

Tumor Microenvironment in Triple-Negative Breast Cancer and Targeting Approaches

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Received 2025 Aug 10
Accepted 2025 Oct 12
Epub ahead of print: December 2025
Published in issue 2026 Feb 15

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Abstract

Triple-negative breast cancer (TNBC) is an aggressive and heterogeneous subtype of breast cancer with high recurrence and early metastasis. Unlike hormone receptor-positive or HER2-positive cancers, TNBC lacks targeted therapies, and standard chemotherapy often yields limited and transient responses, making treatment challenging. The tumor microenvironment (TME) plays a central role in TNBC progression, immune evasion, and therapy resistance. It comprises multiple cellular components, tumor-associated macrophages (TAMs), cancer-associated fibroblasts (CAFs), tumor-infiltrating lymphocytes (TILs), and myeloid-derived suppressor cells (MDSCs), as well as structural and signaling elements such as the extracellular matrix (ECM), growth factors, and cytokines. Interactions among these components create an immunosuppressive, pro-tumorigenic milieu that supports cancer cell survival, invasion, and metastasis. Targeting the TME has emerged as a promising therapeutic strategy. Immunotherapies, particularly immune checkpoint inhibitors (ICIs), can restore antitumor immunity by reversing T cell exhaustion and mitigating immune suppression. Response rates remain variable, leading to the exploration of combination approaches that pair ICIs with chemotherapy, radiotherapy, or TME-modulating agents to enhance efficacy. Direct targeting of TME components, including CAFs, TAMs, MDSCs, and ECM remodeling enzymes, is also being developed to disrupt the supportive tumor niche and enhance drug delivery. This review provides a comprehensive overview of the TNBC TME, emphasizing its role in tumor progression and therapy resistance, and summarizes current and emerging strategies to target the TME. By clarifying complex cellular and molecular interactions, these approaches aim to sensitize tumors to therapy, prevent metastasis, and support the development of more effective, personalized treatments for TNBC.

Keywords: Tumor microenvironment, triple-negative breast cancer, targeting therapy, immune checkpoint inhibitors, drug resistance, biomarkers.

1. Introduction

Global breast cancer incidence rates are increasing, accounting for 31% of female cancers, and the disease burden is projected to rise by 40% by 2040 (1, 2). Triple-negative breast cancer (TNBC) lacks estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) expression (3, 4). TNBC is the most aggressive breast cancer subtype, representing 10-15% of all breast cancer cases globally (5-8). TNBC is classified into four molecular subtypes under the TNBCtype-4 scheme: basal-like 1 (BL1), basal-like 2 (BL2), mesenchymal (M), and luminal androgen receptor (LAR) (9). These subtypes have distinct characteristics and different responses to therapy and prognosis (9-11) (Figure 1). Approximately 25% of TNBC patients have germline BRCA1/2 mutations (12). The absence of conventional therapeutic targets renders TNBC difficult to manage, with treatment primarily dependent on traditional chemotherapy that often yields limited efficacy. Consequently, TNBC is associated with high recurrence and metastasis rates, resulting in poor patient prognosis (13-18). For advanced-stage TNBC, the median survival remains less than 24 months (19-22).

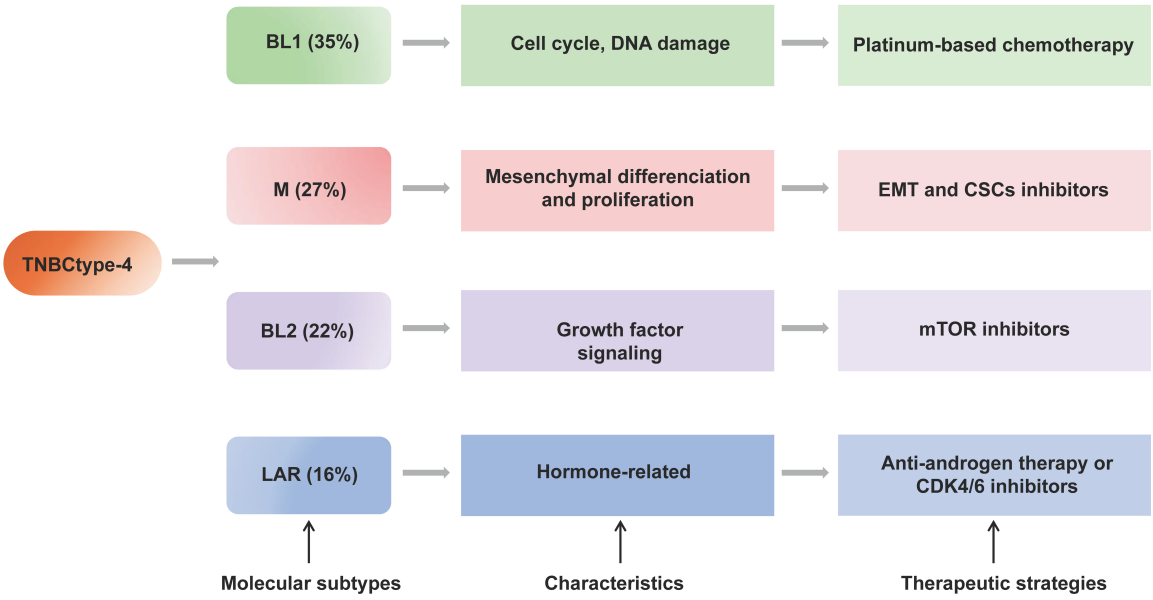

Figure 1: Molecular subtypes, characteristics, and potential therapeutic strategies of TNBC. *This schematic depicts the four main TNBC subtypes under the TNBCtype-4 classification, highlighting their biological pathways and corresponding therapies. Basal-Like 1 (BL1, ~35%) exhibits increased cell-cycle and DNA-damage response, suggesting sensitivity to platinum chemotherapy and other DNA-damaging agents. Basal-Like 2 (BL2, ~22%) exhibits active growth factor signaling, making it a potential target for mTOR inhibitors. The Mesenchymal (M, ~27%) subtype drives epithelial-to-mesenchymal transition (EMT); therapies may target EMT or cancer stem cells (CSCs). Luminal Androgen Receptor (LAR, ~16%) is linked to androgen receptor (AR) signaling, suggesting potential for anti-androgen therapy. BL1: basal-like 1, BL2: basal-like 2, M: mesenchymal, LAR: luminal androgen receptor, EMT: epithelial-to-mesenchymal transition, CSCs: cancer stem cells.*

TNBC's heterogeneity spans clinical, histopathological, and molecular features, marked by high genomic instability and mutation rates (13, 23, 24). TNBC has a greater tumor mutational burden (25), which increases neoantigen production and the chances of immune detection (26). Yet, immunotherapy for TNBC is limited by low immunogenicity and an immunosuppressive tumor microenvironment (TME) (27). These features increase both neoantigen generation and immunogenicity, suggesting

potential for immunotherapy (28, 29). However, complexity makes effective treatment strategies challenging. The TME heavily influences TNBC's progression, immune evasion, and treatment resistance (14, 15). It is a complex, dynamic environment of diverse cellular and non-cellular components that interact closely with tumor cells (17, 30, 31). The TME contains immune cells like tumor-associated macrophages (TAMs), regulatory T cells (Tregs), tumor-infiltrating lymphocytes (TILs), and myeloid-derived suppressor cells (MDSCs), together with stromal cells, cancer-associated fibroblasts (CAFs), endothelial cells, extracellular matrix (ECM), and factors like cytokines, chemokines, and growth factors (32-39) (Figure 2). TNBC TME is especially heterogeneous, with an immunosuppressive profile that promotes tumor growth and treatment resistance (34, 40, 41).

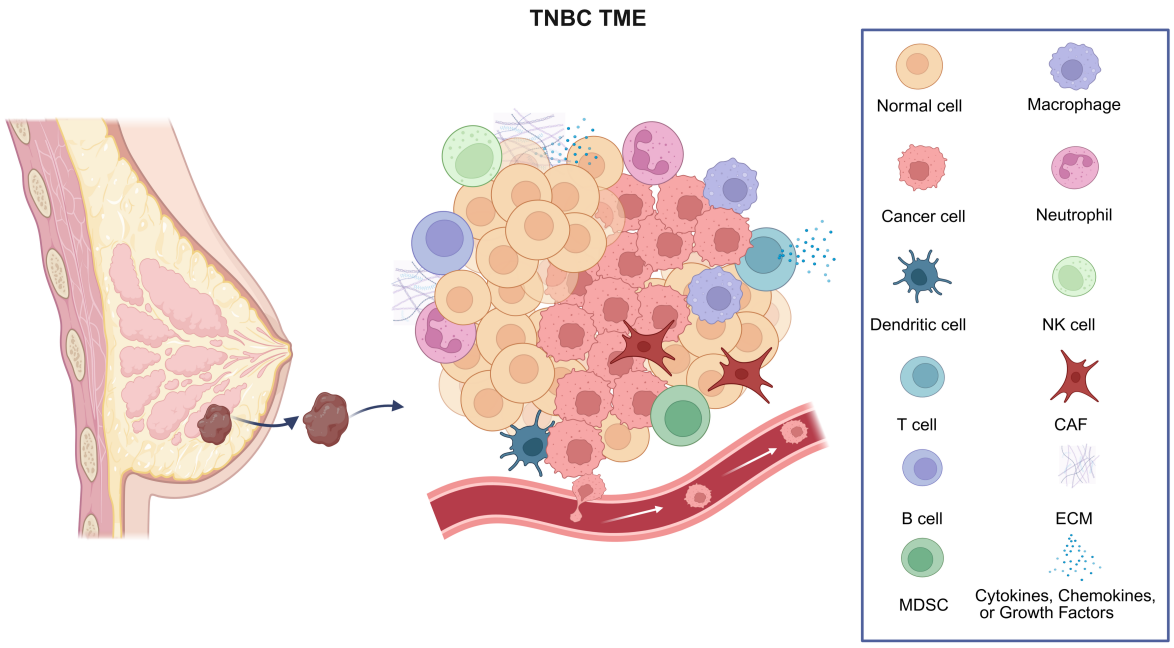

Figure 2: Components of the TNBC TME. *The TNBC TME is a diverse ecosystem that tumor cells use to promote growth and evade immunity. It includes many cellular and non-cellular elements, creating an immunosuppressive environment. Components are macrophages, CAFs, ECM, MDSCs, T cells, B cells, DCs, NK cells, neutrophils, and soluble factors like cytokines, chemokines, and growth factors. TNBC: triple-negative breast cancer, TME: tumor microenvironment, CAF: cancer-associated fibroblast, ECM: extracellular matrix, MDSC: myeloid-derived suppressor cell, DC: dendritic cell, NK: natural killer. Figure created using BioRender.*

Given the limited conventional treatments and the TME's central role, research now focuses on targeting the TME to enhance anti-tumor immunity and overcome resistance (3, 15). Immunotherapies, especially immune checkpoint inhibitors (ICIs), are promising for restoring anti-tumor immune responses and are changing care in early and metastatic TNBC (15, 28, 42). However, not all patients respond to ICIs (response rate 5–23%) (43-47). Resistance remains a significant challenge; therefore, a better understanding of the TME and the development of combination approaches are crucial for improving therapy. New strategies target TME components such as TAMs, CAFs, and MDSCs, or target the ECM, inhibit angiogenesis, or alter tumor metabolism, often in combination with immunotherapy or chemotherapy (38, 48-51).

This review utilizes the TNBCtype-4 molecular subtyping system, which categorizes TNBC into four tumor-intrinsic subtypes: basal-like 1 (BL1), basal-like 2 (BL2), mesenchymal (M), and luminal androgen receptor (LAR). This classification represents a refinement of the earlier TNBC-type system. The rationale for this consolidation is supported by histopathological analyses, which revealed that the transcriptional profiles of the previously defined immunomodulatory (IM) and mesenchymal stem-like (MSL) subtypes were not derived from the tumor epithelium (9). Instead, the IM signature was

predominantly attributable to infiltrating lymphoid cells, while the MSL signature originated from tumor-associated stromal cells. Consequently, the TNBC-type-4 system provides a more accurate representation of tumor cell-specific biology, making it a robust framework for analyzing how intrinsic cancer cell pathways dictate interactions with the surrounding tumor microenvironment and influence therapeutic vulnerabilities.

2. Understanding the Tumor Microenvironment in Triple-Negative Breast Cancer

The TME in TNBC is highly complex and heterogeneous, exerting a significant influence on tumor behavior and therapeutic response (13, 14, 52, 53). Compared to hormone receptor-positive or HER2-positive breast cancers, TNBC demonstrates more extensive interactions with its microenvironment, marked by abundant immune cell infiltration and a dynamic stromal compartment (15, 28, 54). This heterogeneity extends beyond genetic and molecular differences within tumor cells to include the diverse composition and spatial organization of TME components (13, 52, 55, 56). A comprehensive understanding of this complexity is essential for the development of effective targeted therapies.

2.1 Cellular Components of the TNBC TME

The cellular landscape of the TNBC TME encompasses a range of immune and stromal cell populations that interact extensively with cancer cells. These interactions can either promote or inhibit tumor growth, significantly affecting therapeutic outcomes.

2.1.1 Tumor-Associated Macrophages (TAMs)

TAMs are among the most abundant immune cell populations in the TNBC TME and play critical, often dual, roles in tumor progression (17, 37, 41, 57, 58). Macrophages are highly plastic and can polarize into different functional phenotypes, broadly classified as M1 (pro-inflammatory, anti-tumor) and M2 (anti-inflammatory, pro-tumor) (17, 37, 41, 59, 60). In the TNBC TME, TAMs are frequently skewed towards the M2 phenotype, promoting tumor growth, angiogenesis, metastasis, and immunosuppression (57, 61). This polarization triggers signaling pathways that further reinforce the same polarized state. For example, cytokines such as IL-4 and IL-13 activate the JAK1/STAT6 pathway (62, 63), while IL-10 activates JAK1/STAT3 signaling (64), leading to the transcriptional upregulation of typical M2 markers, including Arginase 1, CD206, and immunosuppressive factors (65). The PI3K/Akt pathway is also a central node that integrates various signals to promote M2 survival and function (66). Studies highlight the intricate crosstalk between TNBC cells and TAMs. For instance, M2-type TAMs promote cancer stemness in TNBC cells by secreting vascular endothelial growth factor A (VEGFA) (17). Conversely, TNBC cells educated by TAMs exhibit elevated VEGFA, which further regulates macrophage polarization, forming a positive feedback loop that strengthens the cancer stem cell (CSC) phenotype via the VEGFA/NRP-1/GAPVD1/Wnt/β-catenin pathway (17).

This study underscores the pro-tumorigenic role of TAMs and the importance of this specific signaling axis in promoting stemness and potentially contributing to an immunosuppressive TME (Figure 3). The persistent activation of these intracellular networks, such as STAT3 and β-catenin, not only maintains the M2 phenotype but also establishes a feed-forward loop that reinforces the immunosuppressive TME (65, 67).The microenvironment of tumor occurrence is particularly rich in CD163+ macrophages, which is associated with poor survival prognosis (68-70). An eNAMPT/Ac-STAT3/DIRAS2 axis was identified in TAM-TNBC cell crosstalk, and CD163+ M2-like TAMs are relevant to unfavorable prognosis in TNBC (57). TNBC cell-conditioned medium induces M2 polarization, and these TAMs secrete eNAMPT, which activates STAT3 in TNBC cells via CCR5, downregulates the cancer suppressor DIRAS2, and increases CCL2 secretion. This creates a feedback loop in which CCL2

recruits more macrophages, thereby perpetuating the pro-tumorigenic environment (57). The eNAMPT-mediated activation of STAT3 is a prime example of a core intracellular signaling network driving tumor progression (57). The polarization of TAMs and the related signaling axes is shown in Figure 3.

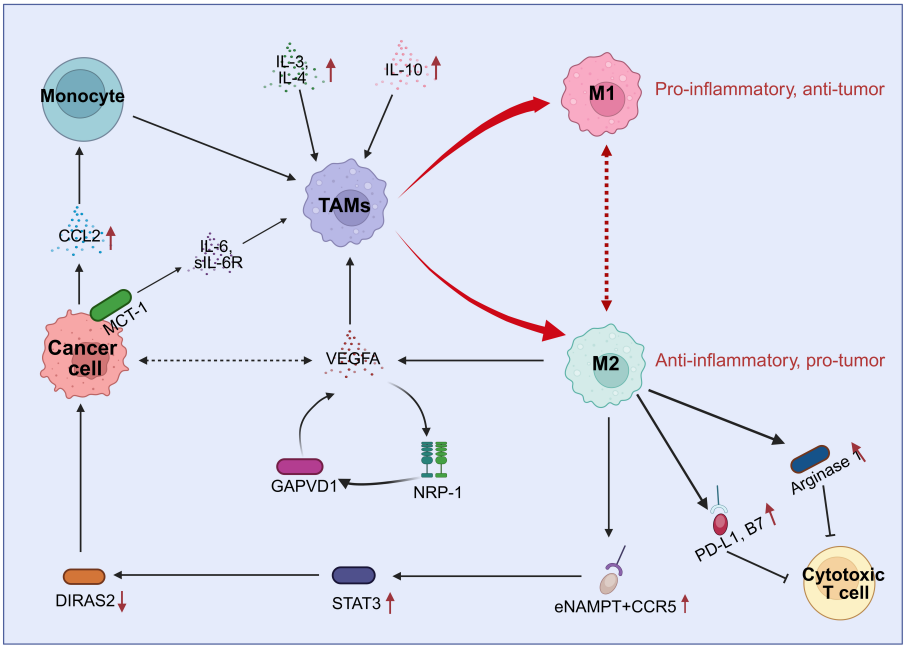

Figure 3: Signaling networks driving M2 polarization of TAMs and their pro-tumorigenic crosstalk with TNBC cells. *Key pathways inducing M2 polarization. Cytokines in the TNBC TME, such as IL-4, IL-13, and IL-10, drive macrophage polarization towards an immunosuppressive M2 phenotype through activation of the JAK1/STAT6 and JAK1/STAT3 signaling axes, respectively. Core feedback loops between M2 TAMs and TNBC cells. Bidirectional crosstalk establishes self-reinforcing, pro-tumorigenic circuits: (i) The VEGFA-Stemness Loop: M2 TAM-derived VEGFA enhances cancer stemness in TNBC cells via the VEGFA/NRP-1/GAPVD1/Wnt/β-catenin pathway. TNBC cells reciprocally upregulate VEGFA, further polarizing TAMs. (ii) The eNAMPT/CCL2-Recruitment Loop: TNBC-conditioned TAMs secrete eNAMPT, which binds CCR5 on TNBC cells to activate STAT3, downregulate the tumor suppressor DIRAS2, and upregulate CCL2 secretion. CCL2 recruits fresh monocytes from the circulation, perpetuating the pool of TAMs for polarization. (iii) The IL-6-Polarization Loop: The oncogene MCT-1 in TNBC cells promotes the secretion of IL-6 and soluble IL-6R (sIL-6R), which accelerates M2 polarization. M2 TAMs, in turn, enhance the invasive potential and stemness of TNBC cells. Immunosuppressive mechanisms. M2 TAMs suppress cytotoxic T cell function through multiple mechanisms, including the expression of immune checkpoint ligands (PD-L1, B7) and metabolic depletion of L-arginine via Arginase 1 activity. TAMs: tumor-associated macrophages, TNBC: triple-negative breast cancer. This figure was created using BioRender.*

The interaction between TNBC cells and TAMs also involves the release of inflammatory cytokines. The oncogene MCT-1 accelerates the polarization of M2-like macrophages by promoting interleukin-6 (IL-6) secretion from TNBC cells (37). This M2 polarization, in turn, enhances the invasive potential of TNBC cells. Furthermore, MCT-1 upregulates soluble IL-6 receptor (sIL-6R) levels, and targeting the IL-6/IL-6R axis effectively suppresses M2 polarization and TNBC stemness (37). The immunosuppressive nature of TAMs represents a significant barrier to effective immunotherapy. Mechanistically, TAMs suppress T cell activity by engaging immune checkpoints, such as PD-L1/PD-1 and CTLA-4/B7, and by metabolically depleting essential amino acids, including L-arginine, through the expression of Arginase 1, a downstream target of STAT3 signaling (71-73). Reprogramming TAMs from an immunosuppressive phenotype to an immune-activating state has been demonstrated to markedly enhance the therapeutic effect of immune checkpoint inhibitors in metastatic TNBC (38).

2.1.2 Cancer-Associated Fibroblasts (CAFs)

CAFs are another significant stromal cell population in the TNBC TME, contributing significantly to ECM remodeling, angiogenesis, immune suppression, and therapeutic resistance (49, 51, 74). CAFs secrete various growth factors, cytokines, and ECM components that create a supportive niche for tumor cells and influence the behavior of other TME components (49, 51, 75, 76). Distinct signaling pathways control the activation and tumor-promoting roles of CAFs. Among these, the TGF-β/SMAD axis is a key regulator, inducing α-SMA expression, a hallmark of CAFs, and stimulating extensive ECM synthesis and remodeling, which contribute to fibrosis and increased tissue rigidity (77-80). This stiffness, in turn, can further activate pro-survival signaling pathways, such as PI3K/Akt, in cancer cells (81).

Epithelial Membrane Protein 1 (EMP1) expression in TNBC cells positively correlates with stromal scores and CAF infiltration. Depletion of EMP1 in TNBC cells significantly inhibited CAF infiltration *in vitro* and *in vivo* (51). From a mechanistic perspective, the knockdown of IL-6 secretion from TNBC cells via the NF-κB pathway hinders CAF proliferation and inhibits TNBC progression and metastasis (51). CAFs also contribute to the physical barrier within the TME and secrete factors, such as transforming growth factor-beta (TGF-β), which promote fibrosis and immunosuppression (49). Beyond TGF-β, CAF-derived exosomes and soluble factors can activate oncogenic pathways in TNBC cells, including the Sonic Hedgehog (SHH) and Hippo/YAP/TAZ pathways, which are critically involved in promoting cancer cell stemness, proliferation, and resistance to chemotherapy (82, 83). Furthermore, CAFs contribute to immunosuppression by secreting cytokines, such as CXCL12, which can exclude T cells from the tumor core, and by expressing enzymes such as indoleamine 2,3-dioxygenase (IDO), which depletes tryptophan and suppresses T cell function (84-86).

2.1.3 Tumor-Infiltrating Lymphocytes (TILs)

TILs, especially cytotoxic T lymphocytes (CTLs), play a vital role in the anti-tumor immune response. The presence and density of TILs in TNBC are frequently associated with a superior prognosis and response to chemotherapy and immunotherapy (15, 28). TNBC is typically characterized by a higher density of TILs in comparison to other breast cancer subtypes, making it potentially more amenable to immunotherapy (15, 28, 87). However, the TME can render these TILs dysfunctional or exclude them from the tumor core, leading to an “immune cold” phenotype despite the presence of lymphocytes (88-90). The immunomodulatory subtype of TNBC is correlated with the highest expression of adaptive immune-related gene signatures. It exhibits a “fully inflamed” spatial pattern, positioning it as the most likely candidate for ICI response (52). In contrast, other subtypes, such as mesenchymal stem-like and luminal androgen receptor subtypes, often exhibit an immunosuppressive or “immune cold” phenotype characterized by stromal and metabolic features, as well as a “margin-restricted” spatial pattern of immune infiltration (52). Mechanisms of immune suppression in the TNBC TME can impair TIL function. C-terminal subunit of MUC1 (MUC1-C), a protein overexpressed in TNBC, links the activation of the interferon-gamma (IFN-γ) pathway to the suppression of the tumor immune microenvironment. MUC1-C activates the JAK1-STAT1-IRF1 signaling pathway, which induces immunosuppressive effectors such as IDO1 and COX2, and is related to the exhaustion and dysfunction of CD8+ T cells (88). This suggests that MUC1-C contributes to the ‘cold’ phenotype and is a promising target for enhancing ICI efficacy (88).

2.1.4 Myeloid-Derived Suppressor Cells (MDSCs)

MDSCs are a heterogeneous population of immature myeloid cells that expand abnormally during cancer and other pathological conditions characterized by chronic inflammation. Within the TME and the peripheral circulation of cancer patients, MDSCs accumulate in large numbers and exert potent

immunosuppressive effects (91, 92). These cells can be broadly classified into two main subsets: polymorphonuclear (PMN-MDSCs), which share phenotypic similarities with neutrophils, and monocytic (M-MDSCs), which resemble monocytes but possess distinct transcriptional and functional profiles. Functionally, MDSCs employ multiple mechanisms to inhibit antitumor immunity. They suppress T cell proliferation and cytotoxic activity by producing reactive oxygen species (ROS), nitric oxide (NO), and arginase-1, which deplete essential amino acids, such as L-arginine and L-cysteine, from the local environment. MDSCs also promote the expansion and activation of Tregs and impair antigen presentation by dendritic cells, further weakening the adaptive immune response. In addition to their immunosuppressive roles, MDSCs contribute to tumor progression by secreting proangiogenic factors such as VEGF and MMP9, enhancing neovascularization and facilitating tumor cell invasion and metastasis. Through these combined mechanisms, MDSCs play a central role in shaping an immunosuppressive TME that enables tumor immune evasion and fosters resistance to various forms of immunotherapy, including immune checkpoint blockade and adoptive T cell transfer (91). Targeting MDSC recruitment, differentiation, or suppressive function is therefore an emerging therapeutic strategy to restore antitumor immunity and improve responses to immunotherapy.

2.1.5 Regulatory T cells (Tregs)

Tregs represent a specialized subset of $CD4^+$ T lymphocytes that play a pivotal role in maintaining immune homeostasis and self-tolerance by suppressing excessive or autoreactive immune responses. The discovery of Tregs and their master transcription factor, FoxP3, a finding recognized by the 2025 Nobel Prize in Physiology or Medicine, highlighted their indispensable role in preventing autoimmunity and revealed their capacity to constrain antitumor immunity when co-opted by the TME. In the context of cancer, Tregs are frequently enriched within the TME, where they suppress cytotoxic T lymphocyte (CTL) activity and dampen the function of natural killer (NK) cells, dendritic cells, and other effector immune populations (34, 93-95). These suppressive effects are mediated by multiple mechanisms, including the secretion of inhibitory cytokines (e.g., IL-10, TGF-β, IL-35), the expression of immune checkpoint molecules (e.g., CTLA-4 and PD-1), and the consumption of essential growth factors such as IL-2, which deprives effector T cells of proliferative signals. In addition, Tregs can induce metabolic suppression via adenosine production and modulate antigen-presenting cell (APC) function, further reinforcing local immunosuppression. Accumulating evidence indicates that elevated Treg infiltration within tumors correlates with poor clinical outcomes and reduced responsiveness to ICIs, particularly in aggressive subtypes such as TNBC (34, 93).

Advanced transcriptomic analyses, including single-cell RNA sequencing and weighted gene co-expression network analysis (WGCNA), have identified gene modules associated with Treg infiltration, demonstrating that high Treg-related scores are predictive of unfavorable prognosis and diminished response to anti-PD-1 immunotherapy (93). Moreover, recent studies have uncovered intriguing interactions between the tumor microbiome and Treg-mediated immune modulation. For instance, *Sphingobacterium multivorum* colonization in TNBC tumors has been shown to accelerate tumor progression and impair anti-PD-1 efficacy, a process linked to increased Treg accumulation and concurrent depletion of $CD8^+$ T cell infiltration (34). These findings underscore the multifaceted role of Tregs as key mediators of immune evasion and resistance to immunotherapy. Consequently, therapeutic strategies aimed at modulating Treg recruitment, stability, or suppressive activity, such as selective depletion within the TME or blockade of Treg-associated checkpoints like cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) and TIGIT, are actively explored to enhance antitumor immune responses and improve the efficacy of current immunotherapeutic regimens.

2.1.6 Other Immune Cells

Beyond the major populations, other immune cells also contribute to the complexity of the TNBC TME. These include dendritic cells (DCs), B cells, neutrophils, and NK cells (13, 35, 96-99). Their roles are multifaceted and can be either pro- or anti-tumorigenic, depending on their phenotype and the specific context of the TME. DCs play a vital role in stimulating adaptive immune responses by presenting tumor antigens to T cells (35, 100). However, the TME can promote the development of tolerogenic DCs (tol-DCs) that suppress anti-tumor immunity (35). Tumors and associated immune cells in TNBC exhibit elevated CD74 expression (35). CD74 expressed on CD11c cells is critical in regulating tumor progression by mediating cross-talk between tumor-infiltrating tol-DCs and regulatory B cells (Bregs) (35). Neutrophils, another myeloid cell type, can also contribute to the immunosuppressive environment, and strategies to modulate their phenotype are being investigated (91). B cells, including Bregs, play a pivotal role in modulating the immune response within the TME (35).

2.2 Non-Cellular Components of the TNBC TME

The non-cellular components of the TNBC TME, including the ECM, soluble factors, and metabolic cues, form the physical and biochemical environment that supports cancer cells and influences cellular interactions.

2.2.1 Extracellular Matrix (ECM)

ECM is a complex network of proteins, glycoproteins, and proteoglycans that not only provides structural support to tissues but also actively regulates cellular behavior through biochemical and mechanical signaling (49, 101). By interacting with cell surface receptors such as integrins and syndecans, the ECM modulates processes including cell proliferation, migration, differentiation, and survival. In addition, the ECM can act as a physical and biochemical barrier, limiting immune-cell infiltration and impeding the penetration of therapeutic agents, including chemotherapeutics and monoclonal antibodies. In TNBC, the ECM is frequently subject to extensive remodeling, resulting in a stiff, dense, and highly cross-linked matrix. This desmoplastic transformation is primarily driven by CAFs, which secrete elevated levels of collagen, fibronectin, laminin, and other ECM components, as well as enzymes such as lysyl oxidase (LOX) and matrix metalloproteinases (MMPs) that remodel and stiffen the matrix (49, 102, 103). The altered ECM architecture not only enhances tumor cell invasion and metastatic potential but also generates elevated interstitial pressure, which can collapse blood vessels and reduce drug delivery. Furthermore, the stiffened ECM promotes mechanotransduction signaling in cancer cells, activating pathways such as YAP/TAZ, FAK, and PI3K/AKT, which contribute to tumor growth, survival, and therapy resistance.

Overall, ECM remodeling in TNBC establishes a tumor-promoting microenvironment that supports malignant progression, facilitates immune evasion, and reduces the efficacy of conventional and targeted therapies, highlighting the ECM as both a prognostic indicator and a therapeutic target (49).

2.2.2 Cytokines, Chemokines, and Growth Factors

Soluble factors within the TME, including vascular endothelial growth factor (VEGF), TGF-β, and IL-6, are secreted by tumor cells, immune cells, and stromal cells, establishing complex communication networks that regulate tumor progression, angiogenesis, and immune evasion (17, 57, 104, 105). These molecules mediate dynamic crosstalk among diverse cell populations, including tumor-associated macrophages, cancer-associated fibroblasts, T cells, and endothelial cells. This interaction shapes tumor architecture, promotes the survival and proliferation of malignant cells, and modulates the immune response, either suppressing or enhancing anti-tumor activity. In addition to cytokines, chemokines such as CXCL8 (IL-8) and CCL2 (MCP-1) play critical roles in recruiting immunosuppressive cells,

promoting angiogenesis, and facilitating metastatic dissemination in TNBC (32, 57, 88, 106). Other soluble mediators, including tumor necrosis factor-alpha (TNF-α) and interferon-gamma (IFN-γ), further influence the TME by regulating immune cell activation, polarization, and trafficking, as well as modulating the expression of adhesion molecules and matrix-remodeling enzymes. Collectively, these factors create a finely tuned, yet highly adaptable, network that governs tumor biology, orchestrates the interplay between immune suppression and activation, and contributes to therapeutic resistance in TNBC.

2.2.3 Metabolic Reprogramming and Hypoxia

Metabolic reprogramming is a defining feature of cancer cells, enabling them to meet the heightened energy and biosynthetic demands of rapid proliferation and survival under stress conditions. Within the TME, metabolic crosstalk between cancer cells and surrounding stromal and immune cells plays a critical role in shaping tumor evolution and modulating immune responses (107). In TNBC, tumor cells frequently exhibit enhanced glycolytic activity, known as the Warburg effect, even in the presence of sufficient oxygen (107). This high glycolytic flux not only generates ATP and biosynthetic precursors required for rapid growth but also leads to lactate accumulation, thereby acidifying the TME. The acidic and nutrient-depleted TME profoundly affects immune cell function. Effector T cells, NK cells, and dendritic cells often experience impaired proliferation, cytokine production, and cytotoxic activity in this environment. In contrast, immunosuppressive populations, such as Tregs and MDSCs, can proliferate (40). Metabolic competition for glucose, amino acids, and other metabolites between cancer and immune cells exacerbates immune dysfunction. Beyond glycolysis, TNBC cells also exhibit alterations in lipid metabolism, glutaminolysis, and oxidative phosphorylation, creating additional layers of metabolic adaptation that support tumor survival, metastasis, and resistance to therapy.

Thus, the interplay between cancer cell metabolism and the TME establishes a metabolic barrier to effective antitumor immunity, highlighting potential therapeutic opportunities to target metabolic pathways in TNBC.

2.2.4 Intratumoral Bacteria

The intratumoral microbiota is now recognized as a key modulator of the TME, with microbial dysbiosis significantly influencing cancer progression and therapeutic response (34, 108-110). Beyond its role in tumorigenesis, the microbiome plays a critical role in determining therapeutic efficacy. It can drive chemoresistance through mechanisms such as *Fusobacterium nucleatum*-induced protective autophagy and *Gammaproteobacteria*-mediated inactivation of gemcitabine (111). Similarly, immunotherapy outcomes are profoundly shaped by the microbiota, which can either enhance antitumor T-cell activity or promote immunosuppression through cytokine signaling pathways. The impact of specific bacteria is often context-dependent. For example, *F. Nucleatum contributes* to tumor development in various cancers through chronic inflammation, immune evasion, and direct cellular interactions. In colorectal and esophageal cancers, it induces autophagy-linked chemoresistance, while in breast cancer, it accelerates progression by reducing T-cell infiltration into the TME (112, 113). Another key player, enterotoxigenic Bacteroides *fragilis*, can colonize breast tissue and promote hyperplasia, growth, and metastasis (114). Notably, anticancer treatments can reciprocally reshape the tumor microbiome. Chemotherapy administration significantly alters the breast tumor microbiome, enriching for specific genera, such as Pseudomonas. The increased abundance of *Brevundimonas and Staphylococcus* in primary tumors is associated with the development of distant metastases, suggesting a potential link between therapy-induced microbial shifts and tumor recurrence (115).

2.2.5 Other Non-Cellular Factors

Various other molecules and pathways contribute to the complexity of the TNBC TME. RNA methylation modifications play a critical role in mediating cellular subtypes and influencing prognosis and immune therapy response in TNBC (116). Targeting Long non-coding RNAs, such as MALAT1, can alter the immune microenvironment, thereby reducing immunosuppression and increasing T-cell infiltration (117). Thymidine Kinase-1 expression is associated with high Treg-cell infiltration and poor prognosis, and may serve as a biomarker and target (93, 118). Lymphocyte activation gene-3, an immune checkpoint protein, is highly expressed in TILs in TNBC and correlates with the ligand programmed death-ligand 1 (PD-L1), suggesting its potential as a target for immunotherapy. However, its prognostic significance requires further investigation (119). CXCL16 and STAT1 signaling in myeloid cells are implicated in immune suppression and resistance to chemotherapy-primed ICI therapy, with STAT1 inhibition showing potential to sensitize TNBC to immune checkpoint blockade (36).

The intricate interplay between cellular and non-cellular components generates a distinct and challenging microenvironment in TNBC. TME heterogeneity complicates the development of effective therapeutic strategies. Tumors may be classified as “hot” (inflamed, high TILs) or “cold” (non-inflamed, low TILs), yet even “hot” tumors can exhibit dysfunctional or excluded immune cells (88, 89). Addressing this complexity requires targeted interventions that modulate specific TME components or pathways to shift the balance toward anti-tumor immunity and overcome resistance.

3. Targeting Approaches to Overcome Immune Escape in the Triple-Negative Breast Cancer Tumor Microenvironment

The efficacy of cancer immunotherapy, particularly ICIs, is profoundly limited by the capacity of tumors to enact a multitude of immune escape mechanisms. These mechanisms, driven by cellular components such as TAMs, MDSCs, and Tregs, as well as physical barriers such as fibrotic ECM and TME metabolic pathways, create an immunosuppressive niche that excludes or inactivates cytotoxic immune cells. Therefore, the next frontier in TNBC therapy lies in developing strategies that build upon the foundation of ICIs by not only unleashing anti-tumor immunity but also systematically dismantling these immune escape pathways. This section reviews therapeutic approaches framed through the lens of overcoming specific immune evasion strategies (Figure 4).

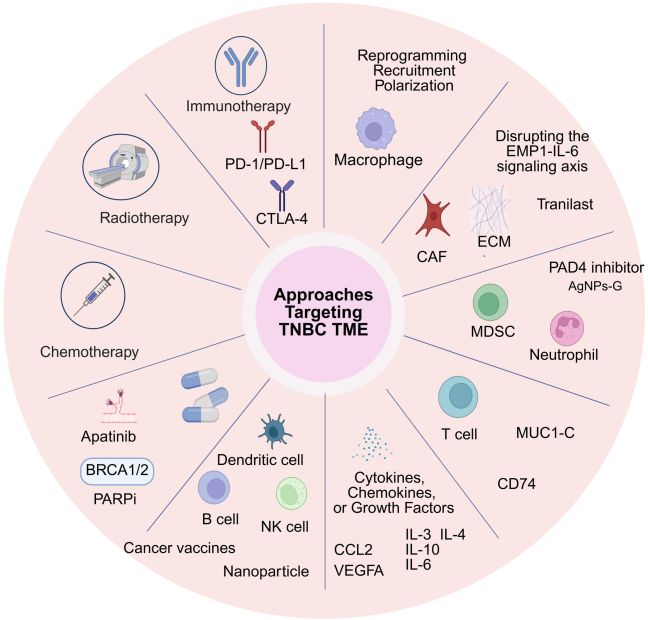

Figure 4: Overview of therapeutic strategies targeting the TNBC TME. *Emerging treatments aim to overcome immunosuppression by targeting key components of the TME. Strategies illustrated include: 1. Immune checkpoint inhibitors (e.g., anti-PD-1 and anti-CTLA-4) to activate T cells; 2. Agents targeting TAMs and MDSCs, and other cells for depletion or reprogramming; 3. Approaches to modulate cancer-associated fibroblasts (CAFs) and the extracellular matrix (ECM); 4. Inhibition of critical cytokine and chemokine signaling networks (e.g., IL-3, IL-4, IL-10, IL-6, and CCL2); 5. Conventional cytotoxic therapies: chemotherapy and radiotherapy; 6. Other novel cell-based therapies. TNBC: triple-negative breast cancer, TME: tumor microenvironment, TAMs: tumor-associated macrophages, MDSCs: myeloid-derived suppressor cells, CAFs: cancer-associated fibroblasts, ECM: the extracellular matrix. This figure was created using BioRender.*

3.1 Immune Checkpoint Inhibitors (ICIs)

ICIs, especially those targeting programmed cell death protein 1 (PD-1) and PD-L1, have shown significant promise in TNBC (14, 48, 120-122). Compared to other breast cancer subtypes, TNBC exhibits superior immunogenicity, characterized by a higher mutation burden and TIL infiltration, making it a suitable candidate for immunotherapy (13, 15, 28). ICIs function by blocking inhibitory signals that hinder T cells from targeting cancer cells and restoring or enhancing anti-tumor immunity (13, 15, 28). The limitations of single-agent ICIs underscore the need for combination strategies. Simultaneously targeting immune checkpoints and modulating the TME can enhance anti-tumor immunity and overcome resistance mechanisms. Clinical evidence supports the use of PD-1/PD-L1 inhibitors in TNBC across early and metastatic stages (123, 124). Still, their efficacy is limited to a subset of patients due to the complex and often immunosuppressive TNBC TME (28, 40, 48). Factors influencing ICI response include the level and spatial distribution of TILs, PD-L1 expression on tumor and immune cells, and the presence of immunosuppressive cell populations and pathways within the TME (28, 52, 88). For example, the immunomodulatory subtype of TNBC, characterized by a "fully inflamed" TME, appears to be the most responsive to ICIs (52). Conversely, the recruitment and activation of immunosuppressive cell populations are primary mediators of ICI resistance. For instance, Tregs directly suppress CTL activity in the TME, while M2-polarized TAMs and MDSCs establish a localized immunosuppressive milieu through cytokine secretion and metabolic dysregulation, such as arginase and IDO (65, 85). Furthermore, the CAF-derived dense ECM creates a physical barrier that impedes T cell infiltration (49, 101). This underscores the need for combinatorial strategies that target these specific escape mechanisms to overcome ICI resistance. In addition to PD-1/PD-L1, other immune checkpoints are being investigated as therapeutic targets in TNBC. Lymphocyte activation gene-3 is another inhibitory receptor expressed on TILs. Its high expression in the TNBC TME, often associated with PD-L1, suggests that dual blockade may benefit certain patients (119). CTLA-4 is a well-established immune checkpoint target, and the combination of anti-CTLA-4 with anti-PD-1 has shown performance in other cancers (49, 107).

3.2 Strategies to Counteract Immune Escape Mechanisms

3.2.1 Reprogramming Myeloid-Driven Immunosuppression

To counteract myeloid-driven immunosuppression, a primary immune escape pathway, several strategies targeting TAMs and MDSCs are in development. Given their prominent role in promoting tumor growth, metastasis, and immunosuppression, TAMs are attractive therapeutic targets in TNBC. Strategies include inhibiting TAM recruitment, depleting TAMs, or reprogramming their phenotype from pro-tumorigenic M2 to anti-tumorigenic M1 (17, 37, 41, 50, 125-127). Targeting the VEGFA/NRP-1/GAPVD1 axis, which facilitates crosstalk between TNBC cells and TAMs and enhances cancer stemness, represents a potential therapeutic strategy (17). Targeting the eNAMPT/CCR5/CCL2 feedback loop between TAMs and TNBC cells, which facilitates M2 polarization and macrophage recruitment, could disrupt the pro-tumorigenic niche (57). Blocking the IL-6/IL-6R axis, which drives M2 polarization and cancer stemness, is another promising approach (37). Using MEK, PPARγ, or HDAC inhibitors to block the MEK/PPARγ/RA signaling axis, which drives M2-type macrophage polarization, represents an encouraging treatment option for modulating the tumor microenvironment and enhancing anti-tumor immunity (128). Novel approaches employing targeted delivery systems are being developed that specifically reprogram TAMs to the M1 phenotype (41, 129, 130). Plant-derived extracellular vesicles (EVs) have also been shown to induce M1 polarization of TAMs, thereby contributing to their antitumor effects (50). A newly developed biomimetic tumor cell membrane-encapsulated nanodelivery system, assembled from a second near-

infrared photothermal agent, chemotherapeutic drugs, and PD-L1 inhibitors coated with TNBC cell membranes, is used to enhance immunotherapy (120). Targeting signaling pathways within TAMs is also being explored. The PI3K-γ inhibitor Eganelisib was shown to reprogram TAMs from an immunosuppressive to an immune-activating phenotype, improving ICI effectiveness in metastatic TNBC (38). TAMs promote epithelial-to-mesenchymal transition (EMT) and strengthen the CSC characteristics in TNBC by activating the CCL2/AKT/β-catenin signaling pathway (131), which could offer novel approaches for diagnosing and treating TNBC. Targeting TAM-specific pathways to influence the TME provides a promising therapeutic strategy.

Targeting immunosuppressive cells such as MDSCs and Tregs to reduce their numbers or suppress their function is critical for enhancing anti-tumor immune responses (91, 93, 132). Targeting specific pathways within these cells, or the factors that recruit them, is a potential strategy. A novel peptidyl arginine deiminase 4 inhibitor has the potential to reshape the phenotype of neutrophils, a subset of MDSCs, and reduce MDSC accumulation (91).

3.2.2 Alleviating Treg-Mediated Inhibition

Strategies aimed at limiting Treg recruitment and suppressive activity represent a promising approach to enhancing antitumor immunity. Tumor cells can actively recruit Tregs through chemokine signaling; for example, CCL20, secreted by tumor cells under the influence of intra-tumoral bacteria, has been shown to promote Treg accumulation in the TME, facilitating immune evasion (34). Inhibiting such chemokine-mediated pathways could therefore reduce Treg-cell infiltration, restore effector T cell function, and increase tumor responsiveness to immunotherapy. In addition to chemokine-driven recruitment, specific molecular markers associated with Treg infiltration and poor clinical outcomes, such as Thymidine Kinase-1 (TK1), have emerged as potential therapeutic targets (93). Modulating these molecules may disrupt pro-tumorigenic interactions between Tregs and other TME components, thereby improving antitumor immune responses and patient outcomes. Moreover, the composition of the TME itself can be therapeutically remodeled to favor effector immune responses. Agents such as silver nanoparticle conjugates (AgNPs-G) have been shown to selectively reduce Treg populations while simultaneously promoting the infiltration and activation of cytotoxic T lymphocytes and other effector immune cells (32). Such strategies highlight the potential of combining TME modulation with direct targeting of Treg recruitment pathways to achieve stronger and more sustained antitumor immunity.

Collectively, these strategies underscore the importance of targeting both the molecular drivers of Treg recruitment and the broader immunosuppressive landscape of the TME as a multifaceted approach to overcome immune evasion in cancer.

3.2.3 Disrupting the Stromal Barrier

CAFs contribute to ECM remodeling, immune suppression, and drug resistance, making them relevant therapeutic targets (49, 51, 133). Strategies include inhibiting CAF recruitment or function and disrupting the CAF-mediated ECM barrier. Targeting EMP1 or disrupting the EMP1/IL-6 signaling axis could reduce CAF infiltration and impede tumor progression (51). Disrupting the ECM and reducing fibrosis, processes often driven by CAFs, can enhance drug delivery and improve immune cell infiltration (49). Inhibiting TGF-β, a key cytokine secreted by CAFs, using Tranilast has been shown to normalize the TME by reducing ECM components, improving perfusion, and facilitating immune cell infiltration (49). Targeting CAFs can also disrupt their role in forming cancer stem cell niches, potentially leading to improved treatment outcomes (134).

3.2.4 Reversing Metabolic Immune Suppression

Metabolic reprogramming in the TME contributes to immune suppression and resistance (135). Inhibiting glycolysis in TNBC cells, for example, by targeting GLUT1, can reduce immunosuppressive factors such as PD-L1 glycosylation and metabolically rewire Tregs, thereby enhancing the ICI response (107). Targeting GLUT3, which is elevated in metastatic TNBC and linked to glycolysis and the inflammatory TME, is another potential metabolic target (106). Modulating the NADPH pathway in tumor cells and the TME can influence redox balance and immune responses, as demonstrated by a nanomedicine that selectively depletes NADPH in tumor cells to enhance low-dose radiotherapy and anti-PD-L1 therapy (40). Inhibiting STAT1 signaling in myeloid cells, which is associated with an immunosuppressive state linked to chemotherapy priming, can sensitize TNBC to immune checkpoint blockade (36). It highlights the importance of targeting metabolic/signaling pathways in immune cells within the TME.

3.2.5 Novel and Emerging Targets

Numerous additional molecules and pathways within the TME are under investigation as therapeutic targets. Targeting the MUC1-C, which promotes immunosuppression by activating the IFN-γ pathway and depleting TILs, could improve ICI efficacy (88). Inhibiting CD74, which induces the expansion of tol-DCs and Bregs, offers a strategy to reverse immunosuppression mediated by these cell types (35). Modulating the AnxA1/FPR1 axis, which interacts with IL-6 signaling and affects TME components like fibroblasts, could also influence tumor progression (104). Targeting long non-coding RNAs, such as Malat1, can alter the immunosuppressive TME and increase T-cell infiltration (117). Inducing pyroptosis in TNBC cells using HDAC inhibitors can promote immune cell infiltration and enhance anti-cancer immunity (136). Targeting intratumoral bacteria, for instance, by killing *F. nucleatum* to release immunopotentiating pathogen-associated molecular patterns (PAMPs), represents a novel strategy to warm up ‘cold’ tumors and enhance immunotherapy (137).

3.3 Combination Approaches

Due to the complexity and redundancy of immunosuppressive mechanisms in the TNBC TME, single-agent therapies frequently demonstrate limited efficacy. Consequently, combination strategies that concurrently target multiple TME components or pathways, or integrate TME targeting with conventional therapies, are under active investigation to improve therapeutic efficacy and address treatment resistance (13, 28, 138, 139).

A cornerstone of this approach is the combination of ICIs with cytotoxic chemotherapy. Chemotherapy can modulate the TME to enhance ICI activity by inducing immunogenic cell death, releasing tumor antigens and damage-associated molecular patterns that stimulate anti-tumor immunity (137) (140). ICIs combined with chemotherapy have shown promising clinical benefit in metastatic and early TNBC (13, 48, 141, 142). However, chemotherapy can also induce immunosuppressive myeloid cells and alter the composition of the tumor microenvironment (36, 143), highlighting the need for rational combinations and timing.

Beyond chemotherapy, combining ICIs with anti-angiogenic agents represents another promising avenue. Anti-angiogenic therapy can reprogram the tumor microenvironment, rendering breast cancer more responsive to PD-1/PD-L1 blockade. Angiogenic factors promote immunosuppression by inhibiting the function of antigen-presenting and effector cells, which in turn drive angiogenesis, perpetuating a vicious cycle of immune dysfunction (144). A phase 2 trial combining Apatinib (a VEGFR2 inhibitor) with Sintilimab (anti-PD-1) and chemotherapy showed a high pathological

complete response rate in early TNBC (48). The incorporation of Camrelizumab (anti-PD-1) and Apatinib demonstrates good tolerance in advanced TNBC, showing promising objective response rates and progression-free survival, regardless of treatment line or PD-L1 expression status (145).

The combination of ICIs with radiotherapy is also under active investigation. Radiation therapy can alter the TME by inducing immunogenic cell death and potentially reversing local immunosuppression, thereby acting as an *in situ* vaccine (14, 146-149). However, the mechanisms underlying radiation resistance and immune changes remain under investigation. Combining low-dose radiotherapy with anti-PD-L1 therapy using a nanomedicine that modulates immunometabolism shows promise in enhancing the efficacy of anti-PD-L1 treatment (40).

To enable these sophisticated combinations, nanomedicine and targeted delivery systems provide a versatile platform. Nanoparticles offer a versatile platform for co-delivering multiple therapeutic agents directly to the TME, overcoming biological barriers, enhancing specificity, and reducing systemic toxicity. These systems increase drug solubility, stability, and circulation time, thereby achieving targeted delivery via the enhanced permeability and retention effect or active targeting of TME components (32, 40, 49, 50, 120, 138, 139, 150-152). Furthermore, nanoparticles can be engineered to be responsive to the distinct properties of the TME, for instance, acidic pH, oxygen deprivation, or heightened enzyme activity, enabling controlled drug release (89, 107, 150).

The combination of ICIs with PARP inhibitors (PARPi) remains an active area of investigation. Preclinical and early clinical data continue to suggest that PARPi can enhance antitumor immunity by increasing PD-L1 expression, creating a rationale for this strategy. Preclinical studies reveal that PARPi exhibit dual immunomodulatory effects: while they can improve tumor immunogenicity by increasing neoantigen exposure and activating STING signaling, they may also upregulate compensatory immune checkpoints, such as PD-L1. However, combining PARPi with PD-1/PD-L1 blockade synergistically enhances T-cell-mediated tumor killing in vivo by overcoming this adaptive resistance (153-155). In a single-arm, open-label, phase 2 trial of niraparib combined with pembrolizumab for advanced or metastatic triple-negative breast cancer, the combination demonstrated a tolerable safety profile and promising antitumor activity, irrespective of BRCA mutation status (156). In BRCA-mutant patients, the MEDIOLA trial (Olaparib plus Durvalumab) achieved a disease control rate of 80% at 12 weeks and 50% at 28 weeks (157). These results confirm the clinical potential of this strategy. However, the phase III KEYLYNK-009 trial (2024), which evaluated niraparib plus pembrolizumab versus chemotherapy in unselected metastatic TNBC, did not meet its primary endpoints of progression-free survival and overall survival in the overall population. Nonetheless, improvements in both progression-free survival and overall survival were observed in patients with tumor BRCA mutations treated with pembrolizumab plus Olaparib, compared to those receiving pembrolizumab plus chemotherapy, suggesting a potential role for this combination as a maintenance strategy in this biomarker-defined subgroup (158).

Furthermore, other emerging multimodal approaches include combining ICIs with cancer vaccines or NK cell therapy (13, 159-163). Combining therapies that induce different forms of immunogenic cell death, such as immuno-chemodynamic therapy enhanced by targeting intratumoral bacteria, can synergistically activate anti-tumor immunity (137). Advanced preclinical models, such as 3D TME-on-a-chip and bioprinted tumor-stroma systems, are revolutionizing our approach to TNBC. They not only elucidate critical tumor-stromal-immune crosstalk but also serve as powerful platforms for evaluating novel therapies and combinations, particularly against therapy-resistant CSCs within their complex microenvironment (164, 165). Strategies that combine targeting CSCs with modulating the TME are also promising, as the TME provides a niche for CSCs and influences their behavior (166-169).

The diverse range of targeting approaches reflects the multifaceted nature of the TNBC TME. Strategies that aim to reprogram or disrupt key TME components, either alone or in combination with ICIs or conventional therapies, have significant potential to improve response rates and overcome treatment resistance. The development of targeted delivery systems, particularly TME-responsive nanoparticles, offers exciting opportunities to enhance the specificity and efficacy of these novel therapies.

Discussion

Despite advances in understanding the TNBC TME and in developing TME-targeted therapies, significant challenges persist. Different TNBC subtypes exhibit distinct TME profiles and varying responsiveness to therapies, emphasizing the need for personalized treatment approaches (52).

Mechanisms of resistance to TME-targeted therapies, including ICIs, are complex and involve multiple redundant pathways and cell populations (15, 28, 54, 170, 171). The plasticity of TME cells, or the dynamic interplay among different immunosuppressive components, can lead to treatment escape (17, 34, 38, 41, 51, 137). Furthermore, the physical barrier imposed by the dense ECM can limit drug penetration and immune cell infiltration, contributing to resistance (101). Metabolic adaptations and hypoxia within the TME also create unfavorable conditions for anti-tumor immunity and can promote resistance to various therapies, including radiation (14, 106, 172-174).

Identifying reliable predictive biomarkers is paramount for stratifying patients and selecting the most appropriate TME-targeted therapies or combinations. While PD-L1 expression is employed as a biomarker for ICI therapy, its predictive reliability is limited, and better markers are needed (15, 28, 175-177). Biomarkers reflecting the overall immune landscape, specific immunosuppressive pathways, or the presence of specific TME components are under investigation (15, 28, 34-36, 51, 88, 93, 119, 178, 179). RNA methylation regulators and oxeiptosis scores are also being explored for their prognostic and predictive potential (48, 180). The application of multi-omics approaches is highly significant for identifying biomarkers that reveal molecular characteristics and key pathways driving TNBC progression and influencing the TME (181, 182).

Future directions in targeting the TNBC TME involve several key areas. Further dissecting the intricate crosstalk between TME components and cancer cells is essential for identifying novel targets and understanding mechanisms of resistance. Developing strategies to reprogram immunosuppressive cells towards an anti-tumor phenotype effectively remains a priority. Targeting the ECM to improve drug delivery and immune infiltration is also crucial. Modulating the metabolic landscape of the TME to favor anti-tumor immunity is another promising avenue. The emerging role of the intratumoral microbiome suggests the development of novel therapeutic strategies. Combination therapies are likely to be the cornerstone of future treatment for TNBC. Rational design of combinations requires a thorough understanding of how different therapies affect the TME and interact with one another.

In conclusion, the TME is a pivotal determinant of TNBC progression, immune evasion, and therapeutic resistance. Targeting the TME, particularly through strategies that enhance anti-tumor immunity and overcome immunosuppression, offers promising avenues for improving TNBC treatment outcomes. While immune checkpoint inhibitors have demonstrated significant potential, their efficacy is often limited by the complex TME. Future efforts should focus on developing rational combination therapies that simultaneously target multiple pro-tumorigenic and immunosuppressive components of the TME. Guided by robust predictive biomarkers, the development of more effective and personalized treatments for TNBC patients can be achieved.

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Declarations

Funding Statement: This work was supported by the National Natural Science Foundation of China (No. 81502260), the Organization Department of Shanghai Municipal Party Committee, Shanghai Science and Technology Commission (No. 23Y11909200 and No. 24SF1900200), Shanghai Xuhui District Science and Technology Committee (No. 23XHYD-06), Chinese Society of Clinical Oncology Foundation (No. Y-2022HER-2AZMS-0349 and No. Y-2023AZMETMS-0077), and Xiamen Haicang District Bureau of Science, Technology, Industry, Information Technology and Commerce (No. 350205Z20242010). We thank the National Natural Science Foundation of China, the Organization Department of the Shanghai Municipal Party Committee, the Shanghai Xuhui District Science and Technology Committee, the Chinese Society of Clinical Oncology Foundation, and the Xiamen Haicang District Bureau of Science, Technology, Industry, Information Technology, and Commerce.

Declaration of Competing Interest: The authors declare no financial or personal relationships with other individuals or organizations that could inappropriately influence or bias the content of this work. All authors have read the final version of the manuscript and confirm that there are no competing interests.

Consent for publication: All authors have approved the final version of the manuscript.

Use of Artificial Intelligence (AI) Disclosure: This article was written by human contributors. Artificial intelligence-based tools were used to improve grammar, language, and readability without affecting the article's scientific content, data interpretation, or conclusions. The authors reviewed and verified all content to ensure its accuracy and integrity.

Dual Use Research of Concern (DURC): "The authors confirm that this research does not constitute DURC as defined by the U.S. Government Policy for Oversight of Life Sciences DURC."

Data Availability Statements (DAS): "No datasets were generated or analyzed in the current study."

Ethics approval and consent to participate: Not applicable, as this study did not involve the conduct of research.

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CRediT authorship contribution statement: Youli Li: Writing – original draft, Writing – review & editing. Yang Chen: Writing – original draft, Writing – review & editing. Yuxin Mu: Writing – review & editing. Xuemei Xiu: Writing – original draft, Writing – review & editing. Wenxind Qin: Conceptualization, Resources, Project administration, Supervision, Writing – original draft, Writing – review & editing. All authors contributed to the work and approved the final version of the manuscript.

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How to cite
Li Y, Chen Y, Mu Y, Xiu X, Qin W. Tumor Microenvironment in Triple-Negative Breast Cancer and Targeting Approaches. Cancer Biome and Targeted Therapy. Published online 2025 Dec.