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Tumor Microenvironment in Breast Cancer Progression and Metastasis: Mechanistic Perspectives

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Abstract Breast cancer progression and metastatic dissemination are not solely determined by intrinsic tumor cell properties but are profoundly influenced by the surrounding tumor microenvironment (TME). The TME comprises a dynamic network of stromal cells, immune infiltrates, endothelial cells, extracellular matrix (ECM), soluble mediators, and metabolic gradients that collectively regulate tumor growth, invasion, angiogenesis, immune evasion, and therapeutic resistance. Reciprocal interactions between malignant epithelial cells and stromal components activate multiple signalling pathways, including TGF-β, PI3K/Akt, NF-κB, Wnt/β-catenin, and hypoxia-inducible factor signalling, which orchestrate epithelial–mesenchymal transition, extracellular matrix remodelling, and metastatic niche formation. Cancer-associated fibroblasts remodel the ECM and secrete pro-tumorigenic cytokines, while tumor-associated macrophages and regulatory T cells suppress anti-tumor immunity and facilitate angiogenesis. Hypoxia and acidic metabolism further enhance genomic instability and drug resistance. Emerging evidence highlights the plasticity of the TME and its role in shaping therapeutic responses, emphasizing the importance of targeting stromal and immune components alongside tumor cells. Advances in single-cell sequencing, spatial transcriptomic, and organoid co-culture models have refined our understanding of cellular heterogeneity and intercellular crosstalk within breast tumors. This review synthesizes mechanistic insights into the cellular, molecular, and biophysical determinants of the breast cancer TME, emphasizing their contribution to invasion and metastasis. Understanding these complex interactions offers opportunities for developing precision therapeutics that modulate the microenvironment to enhance treatment efficacy and overcome resistance.

Keywords: Tumor microenvironment; Breast cancer; Metastasis; Immune modulation; Extracellular matrix.

Introduction

Breast cancer remains the most frequently diagnosed malignancy among women worldwide and represents a leading cause of cancer-related mortality. While substantial progress has been made in early detection and targeted therapies, metastatic disease continues to account for the majority of breast cancer deaths [1]. Traditional cancer models focused primarily on genetic alterations within malignant epithelial cells; however, it is now widely recognized that tumor progression is driven by a

complex ecosystem known as the tumor microenvironment (TME). The TME includes fibroblasts, immune cells, endothelial cells, pericytes, adipocytes, extracellular matrix components, soluble growth factors, cytokines, and metabolic gradients that dynamically interact with tumor cells [2].

These interactions are bidirectional and evolve throughout tumor development. Cancer cells actively remodel their microenvironment by secreting matrix-degrading enzymes, angiogenic factors, and immunomodulatory molecules, while stromal cells reciprocally influence tumor proliferation, survival, and migration. The heterogeneity of the TME contributes to phenotypic diversity within tumors, enabling adaptive responses to therapeutic pressure and environmental stress [3]. In breast cancer, molecular subtypes such as hormone receptor-positive, HER2-enriched, and triple-negative tumors exhibit distinct microenvironmental compositions and immune landscapes, influencing clinical outcomes and responsiveness to therapy [4].

Metastasis involves a multistep cascade that includes local invasion, intravasation, survival in circulation, extravasation, and colonization of distant organs. Each step is regulated by microenvironmental cues, including extracellular matrix stiffness, hypoxia, chemokine gradients, and immune surveillance [5]. The formation of pre-metastatic niches in organs such as bone, lung, liver, and brain further illustrates the systemic influence of the primary tumor on distant microenvironments [6].

Recent technological advances, including single-cell RNA sequencing, spatial omics, and three-dimensional co-culture systems, have provided unprecedented resolution into cellular interactions within the TME. These approaches reveal extensive functional plasticity among stromal and immune populations, highlighting new therapeutic vulnerabilities [7]. Targeting the TME has emerged as a complementary strategy to conventional cytotoxic and targeted therapies, with immune checkpoint inhibitors, anti-angiogenic agents, and stromal modulators entering clinical practice [8]. This review explores the mechanistic basis of TME-driven breast cancer progression and metastasis, emphasizing translational implications for therapeutic intervention.

Cellular Composition of the Breast Cancer Tumor Microenvironment

The cellular architecture of the breast cancer TME is highly heterogeneous and dynamically regulated. Cancer-associated fibroblasts (CAFs) represent a dominant stromal population and actively remodel the extracellular matrix while secreting growth factors such as TGF-β, hepatocyte growth factor, and fibroblast growth factors that enhance tumor proliferation and invasion [9]. Immune infiltrates include tumor-associated macrophages (TAMs), myeloid-derived suppressor cells, regulatory T cells, cytotoxic T lymphocytes, and natural killer cells. TAMs often exhibit an M2-like phenotype that promotes angiogenesis, immune suppression, and metastatic dissemination through secretion of vascular endothelial growth factor (VEGF), interleukin-10, and matrix metalloproteinases [10].

Endothelial cells and pericytes regulate tumor angiogenesis and vascular permeability, facilitating tumor cell intravasation and drug delivery heterogeneity [11]. Adipocytes in the breast microenvironment contribute lipids and adipokines that support metabolic reprogramming and inflammatory signaling in cancer cells [12]. Crosstalk among these cellular compartments generates feedback loops that sustain tumor growth and shape immune evasion. The relative abundance and spatial organization of these populations strongly correlate with prognosis and therapeutic responsiveness in breast cancer patients [13].

Extracellular Matrix Remodeling and Mechanotransduction

The extracellular matrix provides both structural support and biochemical signaling cues that regulate tumor behavior. In breast cancer, excessive deposition of collagen, fibronectin, and laminin increases tissue stiffness and activates integrin-mediated signaling pathways that promote migration and invasion [14]. CAFs and tumor cells secrete matrix metalloproteinases that degrade basement membranes, enabling local invasion and release of matrix-bound growth factors [15].

Mechanical forces generated by a stiffened matrix activate focal adhesion kinase, Src, and Rho GTPase signaling, enhancing cytoskeletal remodeling and epithelial–mesenchymal transition (EMT) [16]. Altered matrix architecture also influences immune cell infiltration and vascular integrity. Increased interstitial pressure limits drug penetration, contributing to therapeutic resistance [17]. ECM-derived fragments can function as bioactive ligands, modulating angiogenesis and inflammation. The dynamic reciprocity between tumor cells and ECM creates a permissive niche for metastatic dissemination, highlighting

mechanotransduction as a critical driver of breast cancer progression.

Immune Modulation and Immune Evasion Mechanisms

Immune surveillance plays a pivotal role in controlling tumor growth, yet breast tumors frequently establish an immunosuppressive microenvironment. TAMs, regulatory T cells, and myeloid-derived suppressor cells suppress cytotoxic lymphocyte activity through checkpoint ligand expression, arginine depletion, and immunosuppressive cytokine release [18]. Programmed death-ligand 1 expression on tumor and stromal cells inhibits T-cell activation, enabling immune escape [19].

Chronic inflammation driven by interleukin-6, tumor necrosis factor-α, and prostaglandins promotes genomic instability and EMT. Conversely, high infiltration of CD8+ T cells is associated with improved prognosis, particularly in triple-negative breast cancer [20]. Immunotherapeutic strategies targeting immune checkpoints and macrophage polarization aim to restore anti-tumor immunity. Understanding immune heterogeneity within the TME is essential for optimizing immunotherapy combinations and identifying predictive biomarkers.

Hypoxia, Metabolic Reprogramming, and Acidosis

Rapid tumor growth often outpaces vascular supply, creating hypoxic and nutrient-deprived microenvironments. Hypoxia-inducible factors activate transcriptional programs that enhance angiogenesis, glycolysis, stemness, and metastatic potential [21]. Cancer cells exhibit aerobic glycolysis, generating lactic acid that acidifies the extracellular milieu and suppresses immune cell function [22].

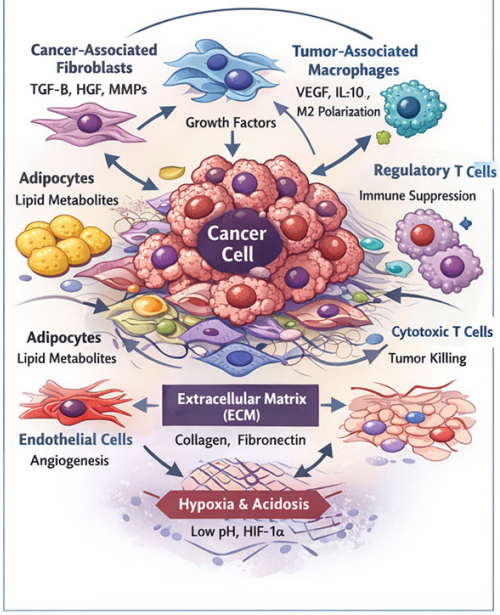
Metabolic coupling between stromal cells and cancer cells supports energy demands and redox balance. Lactate shuttling and lipid transfer from adipocytes fuel oxidative metabolism in metastatic cells. Hypoxia-driven signaling also induces drug resistance by altering transporter expression and promoting quiescent cell populations. Targeting metabolic vulnerabilities within the TME represents a promising therapeutic avenue.

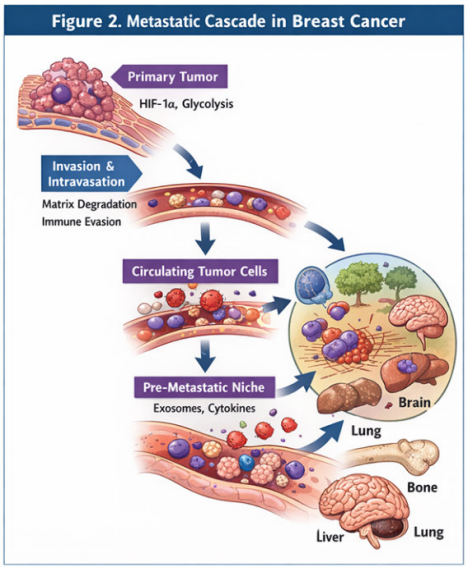
Angiogenesis and Vascular Heterogeneity

Tumor angiogenesis is essential for oxygen and nutrient delivery and is primarily regulated by VEGF, angiopoietins, and platelet-derived growth factor signalling [23]. However, tumor vasculature is structurally abnormal, characterized by irregular branching, leakiness, and impaired perfusion. These features facilitate tumor cell intravasation while limiting immune cell infiltration and drug delivery.

Endothelial cells within the TME acquire pro-tumorigenic phenotypes and contribute to immunosuppression. Anti-angiogenic therapies transiently normalize tumor vasculature, improving therapeutic penetration but may also induce adaptive resistance mechanisms. Vascular heterogeneity influences metastatic organotropism and therapeutic response variability among patients.

Figure 1. Breast Cancer Tumor Microenvironment





Pre-Metastatic Niche Formation and Organotropism

Primary breast tumors secrete extracellular vesicles, cytokines, and matrix-modifying enzymes that condition distant organs before tumor cell arrival [24]. Bone marrow-derived cells are recruited to these sites, establishing a supportive niche characterized by immune suppression, angiogenesis, and matrix remodelling. Organ-specific microenvironments dictate metastatic colonization patterns, with bone, lung, liver, and brain exhibiting distinct molecular landscapes. Chemokine gradients and adhesion molecules facilitate selective homing of circulating tumor cells. Understanding pre-metastatic niche biology offers opportunities for early intervention and metastasis prevention strategies [25].

Table 1. Major Cellular Components of the Breast Cancer Tumor Microenvironment and Their Functions

Cell Type	Key Functions	Impact on Tumor
Cancer-associated fibroblasts	ECM remodelling, growth factor secretion	Invasion, drug resistance
Tumor-associated macrophages	Angiogenesis, immune suppression	Metastasis
Endothelial cells	Vascular formation	Nutrient supply
Adipocytes	Lipid transfer, inflammation	Metabolic support
T lymphocytes	Immune surveillance	Tumor control

Table 2. Key Signalling Pathways Activated in the Tumor Microenvironment

Pathway	Major Role
TGF-β	EMT, fibrosis
PI3K/Akt	Survival, metabolism
NF-κB	Inflammation
HIF-1α	Hypoxia adaptation
Wnt/β-catenin	Stemness

Conclusion

The tumor microenvironment plays a decisive role in breast cancer progression, metastasis, and therapeutic resistance. Complex interactions between malignant cells and stromal, immune, vascular, and extracellular matrix components regulate invasion, immune evasion, metabolic adaptation, and metastatic niche establishment. Mechanistic insights into these processes have transformed the understanding of breast cancer from a cell-autonomous disease to a systemic, ecosystem-driven pathology. Therapeutic strategies targeting angiogenesis, immune checkpoints, stromal remodelling, and metabolic vulnerabilities highlight the translational potential of TME-focused interventions. However, heterogeneity and plasticity within the microenvironment pose challenges to durable therapeutic responses. Integration of spatial biology, systems modelling, and precision medicine approaches will enable patient-specific micro environmental profiling and rational combination therapies. Continued investigation into TME dynamics is essential for improving long-term outcomes and preventing metastatic disease.

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