Breast Cancer Molecular Subtypes Shape Mast Cell Functional Plasticity: Research Advances in Dual Tumor-Promoting and Tumor-Suppressing Mechanisms Postprint

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Abstract

Breast cancer, as a highly heterogeneous malignant tumor, exhibits development that is closely associated with the dynamic regulation of immune cells within the tumor microenvironment (TME). Mast cells (MCs), serving as key immune cells with functional plasticity in the TME, have their functions co-regulated by spatial localization and breast cancer subtypes, manifesting dual tumor-promoting and tumor-suppressing effects. This article systematically reviews the recruitment mechanisms, tumor-promoting roles, and tumor-suppressing roles of MCs in breast cancer, with particular emphasis on dissecting the functional heterogeneity of MCs across Luminal, HER2-overexpressing, and triple-negative breast cancer (TNBC) subtypes. This review demonstrates that the dual role of MCs is jointly determined by their subpopulation heterogeneity, microenvironmental cues, and breast cancer subtype specificity, wherein antigen-presenting MCs (apMCs) play a pivotal role in immune sensitization of TNBC. This study provides a theoretical foundation for targeting MCs to modulate specific subpopulations, block tumor-promoting pathways, or enhance antigen-presenting function, thereby reversing drug resistance and optimizing combined immunotherapy.

Full Text

Preamble

Functional Plasticity of Mast Cells Shaped by Breast Cancer Subtypes: Dual Pro- and Anti-Tumor Roles

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Abstract
Breast cancer is a highly heterogeneous malignant tumor whose progression is closely associated with the dynamic regulation of immune cells within the tumor microenvironment (TME). Mast cells (MCs), as key immune cells with functional plasticity in the TME, display dual roles in either promoting or suppressing tumor growth, which are co-regulated by their spatial localization and the specific breast cancer subtype. This article provides a systematic review of the recruitment mechanisms of MCs, as well as their pro-tumorigenic and anti-tumor functions in breast cancer, with particular emphasis on elucidating the functional heterogeneity of MCs across Luminal, HER2-positive, and triple-negative breast cancer (TNBC) subtypes. This study demonstrates that the dual functions of MCs are collectively determined by subpopulation heterogeneity, microenvironmental signals, and breast cancer subtype specificity. Notably, antigen-presenting MCs (apMCs) play a central role in immune sensitization in TNBC. This study offers a theoretical foundation for targeting specific MC subpopulations to inhibit pro-tumor pathways or enhance antigen presentation, thereby reversing drug resistance and improving combination immunotherapy strategies.

Keywords
Breast cancer; Mast cells; Tumor microenvironment; Molecular subtypes; Review

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1 Literature Search Strategy

A computerized search of the PubMed database was conducted from inception to July 2025 using the following English search strategy: ("Breast Cancer" OR "Breast Carcinoma") AND "Mast Cell" . This initial search yielded 152 articles. Inclusion criteria comprised studies investigating the impact of MCs on breast cancer, mechanisms of MC alterations within the TME, and interactions between MCs and other immune cells. Exclusion criteria included insufficient relevance to the topic, methodological quality defects, and inaccessible full texts. Ultimately, 45 articles were included in this review.

2 Biological Characteristics of MCs and Their Recruitment and Activation in the TME

MCs are bone marrow-derived immune cells whose remarkable phenotypic heterogeneity and functional plasticity underlie their dual roles in the TME [**?**]. This heterogeneity manifests as differences in gene expression, receptor profiles, and mediator storage reservoirs influenced by various tissues and individual factors [**?**, **?**]. MC-stored mediators include preformed substances such as histamine, tryptase, and chymase, as well as newly synthesized mediators like interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), stromal cell-derived factor-1 (SDF-1), prostaglandin D2 (PGD2), and leukotriene C4 (LTC4) [**?**]. These mediators can broadly activate neighboring immune cells (e.g., macrophages) and structural cells (e.g., fibroblasts, endothelial cells), thereby regulating inflammatory responses, angiogenesis, and tissue remodeling processes [**?**]. Since histamine and tryptase are also core mediators of allergic reactions, this intrinsic plasticity enables MCs to execute seemingly opposite functions depending on local environmental demands—for instance, rapidly releasing histamine to trigger inflammation during allergic responses while participating in complex immune homeostatic regulation within the breast cancer TME [**?**].

In the breast cancer TME, MC recruitment is primarily driven by key chemokine signaling axes, particularly the stem cell factor (SCF)/c-Kit receptor and SDF-1/C-X-C chemokine receptor type 4 (CXCR4) pathways [**?**]. Breast cancer tissues highly express SDF-1 and its receptor CXCR4. On MC surfaces, CXCR4 functions as a G protein-coupled receptor that, upon SDF-1 binding, triggers downstream signaling cascades involving phospholipase C (PLC)/protein kinase C (PKC), phosphatidylinositol 3-kinase (PI3K)/protein kinase B (AKT), and mitogen-activated protein kinase (MAPK), thereby promoting MC chemotaxis, migration, and proliferation toward tumor sites [**?**]. Concurrently, SCF binding to the c-Kit receptor activates extracellular signal-regulated kinase (ERK) and PI3K pathways, which not only mobilize MC precursors from the bone marrow

to the TME but also enhance their survival [**?**]. Dysfunctional c-Kit can further promote MC enrichment in breast cancer, thereby regulating tumor progression. Notably, tumor-derived factors in the TME can amplify the CXCL12/CXCR4 axis through ERK/nuclear factor kappa-B (NF- B), forming a positive feedback loop that optimizes MC infiltration density and localization within tumor parenchyma [**?**, **?**, **?**].

Once recruited to the TME, MC phenotype and function undergo dynamic regulation by complex microenvironmental signals. Cytokines can directly trigger MC degranulation via the Fc epsilon receptor I (Fc RI), which confers anti-tumor potential but also serves as a central mechanism for systemic allergic reactions [**?**]. Additionally, the hypoxic microenvironment of the breast cancer TME differentially regulates CXCR4 expression through the hypoxia-inducible factor-1α (HIF-1α) pathway, influencing MC spatial distribution heterogeneity [**?**]. In chronically hypoxic perivascular regions, MCs can upregulate CXCR4 via the epidermal growth factor receptor (EGFR)/HIF-1α axis, promoting their aggregation around blood vessels and participation in vascular remodeling and aberrant neovascularization [**?**]. In contrast, within the tumor core, HIF-1α-activated CXCR4-high MCs tend to infiltrate the tumor parenchyma, where they interact with tumor cells or regulatory T cells (Tregs) through the CXCL12/CXCR4 axis to establish an immunosuppressive microenvironment [**?**]. Furthermore, fibrin in the extracellular matrix (ECM) can influence MC adhesion, degranulation patterns, and mediator release through integrin signaling [**?**]. It is the integration of these microenvironmental signals that determines the dual role of MCs in the breast cancer TME. On one hand, they can promote tumor progression by releasing VEGF, MMP-9, and immunosuppressive factors such as IL-10 and transforming growth factor-β (TGF-β), thereby stimulating angiogenesis, tumor invasion, and metastasis while recruiting Tregs or MDSCs to create an immunosuppressive milieu [**?**]. On the other hand, under specific conditions, the apMC subset can release pro-inflammatory factors such as IL-1β, IL-12, TNF-α, and chemokines that directly kill tumor cells or activate natural killer (NK) cells, dendritic cells (DCs), and T cells (particularly Th1-type) to enhance anti-tumor immune responses [**?**]. Therefore, the ultimate effect of MCs in breast cancer represents the integrated outcome of their intrinsic heterogeneity, recruitment dynamics, and TME signaling, reflecting their high functional plasticity and context dependency. Consequently, targeting MCs therapeutically requires precise modulation of their pathological versus physiological activation.

3 Molecular Mechanisms of MC-Mediated Pro-Tumor Effects in Breast Cancer

3.1 Promoting Angiogenesis

3.1.1 MCs Release Pro-Angiogenic Factors to Drive Breast Tumor Vascularization MCs in the breast cancer TME drive tumor vascular network formation and expansion by releasing multiple pro-angiogenic factors, including VEGF and basic fibroblast growth factor (bFGF). MCs secrete VEGF, which directly activates VEGFR2 receptors on endothelial cells to promote their proliferation, migration, and tube formation [**?**]. VEGF also enhances its pro-angiogenic effects by stabilizing transglutaminase 2 (TGase 2) in the ECM [**?**]. Clinical studies have demonstrated that VEGF expression levels in breast cancer significantly correlate with tumor vascular density, metastatic risk, and poor prognosis [**?**]. Additionally, bFGF released by MCs synergizes with bFGF secreted by tumor cells and cancer-associated fibroblasts to activate FGFR signaling pathways that promote endothelial cell proliferation [**?**]. bFGF can also upregulate VEGF expression, creating a pro-angiogenic cascade [**?**]. Moreover, MC-derived neuropeptide Y (NPY) increases VEGF and bFGF secretion through Y receptors (YRs) [**?**]. These factors collectively stimulate endothelial cell proliferation, migration, and vessel formation, ensuring adequate nutrient supply for tumor cell growth and survival, thereby reinforcing the malignant phenotype of breast tumors.

3.1.2 MC Proteases Release Pro-Angiogenic Fragments Through ECM Degradation In the breast cancer TME, MCs are activated by tumor-derived signals such as SCF, IL-33, and hypoxic conditions via both Fc RI-dependent and -independent pathways, leading to degranulation and release of proteases like tryptase and chymase [**?**]. These MC proteases drive breast cancer angiogenesis by directly degrading ECM components to release pro-angiogenic fragments. Tryptase, as a core effector molecule, specifically cleaves ECM components such as fibronectin and type IV collagen, disrupting basement membrane structural integrity [**?**]. Simultaneously, chymase activates matrix metalloproteinases (MMP-2/9), synergistically expanding ECM degradation. This dual action not only directly releases stored pro-angiogenic factors like VEGF from the ECM but also exposes cryptic matrix-derived epitopes that provide chemotactic signals for endothelial cell migration [**?**]. Clinical studies have further indicated that MC-mediated ECM remodeling positively correlates with microvascular density, particularly in stromal regions where high tryptase activity is directly associated with aggressive tumor progression [**?**, **?**]. In summary, MC-driven ECM remodeling represents a critical link in the cascade of tumor neovascularization in breast cancer (Figure 1 [Figure 1: see original paper]).

3.1.3 Pro-Angiogenic Capacity of MCs Varies Across Breast Cancer Subtypes The pro-angiogenic capacity of MCs exhibits significant het-

erogeneity across breast cancer subtypes. Basal-like/TNBC subtypes, characterized by high angiogenic demands, show prominent tumor progression driven by MC-released pro-angiogenic mediators such as VEGF [**?**]. Particularly in basal-like 1 (BL1) and basal-like 2 (BL2) subtypes, MC infiltration correlates strongly with increased vascular density, metastatic propensity, and poor prognosis [**?**]. This pro-angiogenic activity is substantially more potent than in Luminal subtypes [**?**], likely reflecting subtype-specific microenvironmental regulation. Although the TGF-β pathway-related molecule N-cadherin is upregulated in TNBC, insufficient MMP2-mediated activation of TGF-β precursors may limit its release, rendering MCs more dependent on direct pro-angiogenic factors like VEGF/bFGF [**?**]. Meanwhile, the high immune infiltration characteristic of TNBC may compel MCs to mediate immune escape through non-TGF-β pathways, indirectly enhancing angiogenic demands. In Luminal B subtypes, downregulated hormone receptors activate the TGF-β pathway, prompting MCs to recruit Treg cells and collaborate with tumor-associated macrophages (TAMs) to construct an immunosuppressive microenvironment that indirectly supports neovascularization [**?**]. In Luminal A subtypes, the presence of the anti-angiogenic factor thrombospondin-1 (TSP-1) restricts MC pro-angiogenic activity, consistent with their relatively better prognosis [**?**, **?**]. These findings demonstrate that differential MC pro-angiogenic functions reflect evolutionary adaptation strategies of distinct subtypes to the TME, suggesting that TNBC may benefit from targeting the MC-VEGF axis, whereas Luminal B may respond to combined TGF-β-MC blockade strategies. This heterogeneity significantly influences the vascular biology and clinical progression of breast cancer.

Note: IL-33 = interleukin-33, SCF = stem cell factor, NPY = neuropeptide Y, YRs = Y receptors, bFGF = basic fibroblast growth factor, VEGF = vascular endothelial growth factor, ECM = extracellular matrix. Arrows indicate promotion.

Figure 1 [Figure 1: see original paper] Pro-angiogenic mechanisms of mast cells

3.2 Driving Invasion and Metastasis

3.2.1 MC-Derived Tryptase Enhances Cancer Cell Invasiveness Through PAR-2 In TNBC models, MC-released tryptase significantly enhances cancer cell pseudopodia formation and migration capacity through protease-activated receptor 2 (PAR-2), an effect reversible by PAR-2 inhibitors [**?**]. Upon PAR-2 activation, G protein-coupled mechanisms trigger downstream signals that include upregulation of pro-inflammatory factors such as TNF-α and IL-8, creating an inflammatory microenvironment [**?**]. Additionally, the p38 MAPK/inducible nitric oxide synthase (iNOS) pathway enhances cancer cell motility [**?**], while forkhead box protein J1 (FoxJ1) pathway disruption compromises cell polarity [**?**]. Tryptase also upregulates the invasion-related protein focal adhesion kinase (FAK); when tryptase activates FAK via PAR-2, FAK phosphorylation further activates the downstream growth factor receptor-bound protein 2 (GRB2)/rat sarcoma (RAS) pathway, augmenting cell motility

and migration [**?**]. Collectively, these findings demonstrate that the MC-driven tryptase-PAR-2 axis constitutes a key molecular hub integrating inflammatory responses, cell polarity disruption, and motility signaling to facilitate breast tumor cell invasion and metastasis.

3.2.2 MC-Derived TGF-$ $1 Induces Epithelial-Mesenchymal Transition in Breast Cancer Cells MC-released TGF-$ $1 is a critical inducer of epithelial–mesenchymal transition (EMT), which significantly correlates with lymph node metastasis and poor prognosis in box binding homeobox 1 (ZEB1) [**?**, **?**, **?**]. Specifically, the TGF– 1/Snail axis directly inhibits E–cadherin, disrupting intercellular junctions, while TGF– 1 induces mesenchymal marker vimentin expression derived TGF– $1-induced Hybrid E/M cells exhibit enhanced invasiveness and metastatic potential, representing a key factor in breast cancer progression (Figure 2 [Figure 2: see original paper]).

Note: MCd = mast cell degranulation, PAR-2 = protease-activated receptor 2, TGF-$ 1 = transforming growth factor– 1, T R /T $R = cell surface receptors, MAPK = mitogen-activated protein kinase, iNOS = inducible nitric oxide synthase, FoxJ1 = forkhead box protein J1, FAK = focal adhesion kinase, GRB2 = growth factor receptor-bound protein 2, RAS = rat sarcoma, PI3K = phosphatidylinositol 3-kinase, AKT = protein kinase B, ZEB1 = zinc finger E-box binding homeobox 1, E-Cad = E-cadherin, Twist = twist-related protein 1, VIM = vimentin. Arrows indicate inhibition.

Figure 2 [Figure 2: see original paper] Mechanisms of mast cells in driving breast cancer cell invasion and metastasis

3.3 Shaping an Immunosuppressive Microenvironment

3.3.1 MCs Release Inhibitory Cytokines MCs can be activated through either the immunoglobulin E (IgE)-dependent classical pathway or alternative pathways, subsequently releasing IL-10. IL-10 directly suppresses CD8+ T cell activity while reducing MDSC infiltration, thereby weakening anti-tumor immune responses [**?**]. Clinical data show that serum IL-10 levels are significantly elevated in breast cancer patients and correlate with the immunosuppressive phenotype of regulatory B cells (Bregs) [**?**]. IL-10 also promotes MC secretion of immunosuppressive molecules such as galectin-9, further inhibiting CD8+ T cell anti-tumor function [**?**]. Prostaglandin E2 (PGE2), an arachidonic acid metabolite catalyzed by cyclooxygenase-2 (COX-2), is upregulated upon MC activation with increased COX-2 expression promoting PGE2 generation [**?**]. Tumor cell-derived PGE2 maintains an immunosuppressive microenvironment through autocrine signaling via prostaglandin E2 receptor 4 (EP4). Blocking PGE2 synthesis enzymes or EP4 receptors can reverse Treg immunosuppressive function [**?**]. Additionally, PGE2 directly regulates DC function by inducing a regulatory DC phenotype through its receptor signaling, thereby promoting tumor progression [**?**]. In summary, MCs serve as key effector molecules in constructing an immune-privileged microenvironment in breast cancer by releasing

inhibitory cytokines IL-10 and PGE2 to suppress T cell activity and remodel myeloid cell function.

3.3.2 MCs Mediate T Cell Exhaustion Through PD-L1 Expression MC-expressed programmed death-ligand 1 (PD-L1) binds to PD-1 on T cells, recruiting Src homology 2 domain-containing protein-tyrosine phosphatase 2 (SHP2) to inhibit zeta-chain associated protein kinase 70 (ZAP70) and PKC phosphorylation downstream of the T cell receptor (TCR), while simultaneously activating the PI3K/AKT pathway [**?**, **?**]. Overactivated AKT inhibits the forkhead box protein O1 (FOXO1) transcription factor, leading to downregulation of effector T cell key genes interferon-γ (IFN-γ) and IL-2, driving T cells into an "exhausted phenotype" with diminished anti-tumor activity [**?**]. In vitro experiments demonstrate that PD-1 antibodies can activate MC PI3K/AKT and calcium signaling pathways, promoting histamine and cytokine release [**?**]. Calcium influx further impairs T cell activation through the calcineurin (CaN)/nuclear factor of activated T cells (NFAT) axis, which inhibits TCR signaling [**?**]. Thus, MC-mediated T cell exhaustion represents a critical mechanism of tumor immune evasion with significant negative impacts on disease progression (Figure 3 [Figure 3: see original paper]).

Note: IgE = immunoglobulin E, PD-L1 = programmed death-ligand 1, PD-1 = programmed death-1, MDSCs = myeloid-derived suppressor cells, CaN = calcineurin, NFAT = nuclear factor of activated T cells, SHP2 = Src homology 2 domain-containing protein-tyrosine phosphatase 2, FOXO1 = forkhead box protein O1, IFN-γ = interferon-γ, COX-2 = cyclooxygenase-2, PGE2 = prostaglandin E2.

Figure 3 [Figure 3: see original paper] Mechanisms of mast cells in shaping the immunosuppressive tumor microenvironment

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4 Molecular Mechanisms of MC Anti-Tumor Effects in Breast Cancer

4.1 MCs Directly Kill Tumor Cells Through Granzyme Release

Granzyme B and granzyme C are serine proteases expressed by MCs that are typically secreted by T cells and NK cells but can also be upregulated in MCs through cytokine stimulation such as IL-33 [**?**]. IL-33 significantly upregulates both mRNA and protein levels of granzyme C in bone marrow-derived mast cells (BMMCs) through p38α/β MAPK and ERK1/2 signaling pathways [**?**]. Specifically, IL-33 activates downstream mitogen- and stress-activated protein kinase 1/2 (MSK1/2) via ERK1/2 and p38, which then phosphorylates the transcription factor cAMP-response element binding protein (CREB). Phosphorylated CREB binds to CREB-binding sites in the granzyme C promoter to enhance its transcription. In mice with MSK1/2 double knockout or CREB Ser133Ala

knock-in, BMMCs completely lose the ability to upregulate granzyme C in response to IL-33. This pathway is crucial, as demonstrated by the loss of IL-33-induced granzyme C upregulation in these genetic models. Granzyme B, the most abundant granzyme, not only exerts direct cytotoxicity by inducing tumor cell apoptosis but also participates in tissue remodeling by cleaving ECM proteins [**?**, **?**]. Notably, the expression regulation mechanisms of granzyme B differ from those of granzyme C in MCs, and upon IL-33 exposure, MCs may preferentially express granzyme C over granzyme B. These two granzymes may act synergistically or independently to exert cytotoxic and tissue remodeling functions within the tumor immune microenvironment.

4.2 MCs and DCs Form a Positive Feedback Loop to Activate Th1 Immune Responses

In breast cancer tissues, close contact between MCs and DCs forms immunological synapses, providing a structural basis for MC-mediated tumor cell killing [**?**]. Specifically, MCs secrete IL-12, a critical Th1-polarizing cytokine that activates the signal transducer and activator of transcription 4 (STAT4) pathway, promoting naive CD4+ T cell (Th0) differentiation into Th1 cells and inducing production of the signature Th1 cytokine IFN-γ [**?**]. IL-12 also enhances DC antigen presentation capacity and directly promotes DC maturation. Mature DCs further secrete IL-12 and IL-18, and are guided by MC-derived cytokines to migrate toward lymph nodes, enhancing the efficiency of initial T cell activation to strengthen Th1 polarization [**?**, **?**]. IFN-γ secreted by Th1 cells can, in turn, activate MCs, forming a positive feedback loop. IFN-γ upregulates major histocompatibility complex (MHC) class II molecules and co-stimulatory molecules (e.g., CD86) on MCs, enhancing their antigen presentation function to promote further Th1 polarization [**?**]. Thus, in breast tumors, MCs may engage in bidirectional signaling crosstalk with DCs to establish a continuously amplified positive feedback loop that effectively drives Th1-type anti-tumor immune responses.

4.3 apMCs Enhance ICI Efficacy

4.3.1 Antigen-Presenting MCs Improve PD-1 Inhibitor Efficacy In breast cancer, apMCs show significant positive correlation with therapeutic response to PD-1/PD-L1 inhibitors. TNBC is an aggressive breast cancer subtype where immune checkpoint inhibitors (ICIs) demonstrate clinical benefit, yet many patients exhibit poor response [**?**]. Studies have found that high-level apMC infiltration improves treatment outcomes in TNBC patients [**?**]. Single-cell transcriptomic analysis of TNBC patient samples revealed that apMCs localize within tertiary lymphoid structures and efficiently execute antigen presentation and cross-presentation functions, expressing key co-stimulatory molecules CD80 and CD86. This promotes activation and expansion of tumor-reactive T cells, thereby enhancing ICI efficacy. Specific deletion of the antigen presentation mechanism in MCs impairs tumor-reactive T cell activity. In an indepen-

dent cohort of 484 TNBC patients, high-level apMCs significantly correlated with enhanced clinical benefit from anti-PD-1 therapy, achieving an objective response rate of 50.0% [**?**]. Moreover, in TNBC mouse models, apMC activation coordinated anti-tumor immune responses by recruiting and activating T and B cells to improve the immune microenvironment [**?**]. These results underscore that apMC abundance may serve as a biomarker for predicting ICI responsiveness in TNBC and provide new directions for immunotherapeutic strategies. However, the IL-33/suppression of tumorigenicity 2 (ST2) pathway that apMCs rely on to enhance PD-1 inhibitor efficacy is also a key driver of allergic diseases, necessitating careful assessment of off-target toxicity risks in clinical translation. Current studies have shown that sST2-Fc or anti-PD-L1-sST2 can remodel the inflammatory tumor microenvironment and generate robust anti-tumor effects, offering potential for therapeutic strategies simultaneously targeting IL-33 and PD-L1 [**?**]. Mechanistically, tumor cell-secreted IL-33 binds to the ST2 receptor on MCs to activate downstream inflammatory sensitization signals including p38 MAPK and NF- B [**?**]. Blocking IL-33/ST2 reduces Treg-mediated immunosuppression, enhances CD8+ T cell activity, improves PD-1 inhibitor efficacy, and remodels the tumor microenvironment from an immunosuppressive to an anti-tumor state.

4.3.2 MCs Bridge Dual-Track Immunity to Enhance ICI Response
MCs bridge innate and adaptive immunity through molecular interaction networks in the breast cancer microenvironment, thereby enhancing ICI efficacy. As versatile innate immune cells in the tumor TME, MCs dynamically regulate immune cell behavior through cytokine and chemokine release. Their expressed Toll-like receptors (TLRs) sense tumor-associated signals to activate innate immune responses, which subsequently enhance ICI effects through direct interactions with adaptive immune cells [**?**, **?**]. This process involves multi-level interactions: MCs actively recruit T and B cells to tumor sites by secreting C-C motif ligand 2 (CCL2) and CCL5, promoting their infiltration and activation. This function has been validated as a key mechanism coordinating anti-tumor responses in TNBC models, significantly improving PD-L1 blockade efficacy by enhancing T cell activation and B cell antibody responses [**?**, **?**]. Simultaneously, apMCs directly present tumor antigens to CD4+ T cells through MHC class II molecules and co-stimulatory molecule CD40, driving adaptive immune responses and establishing MCs as dynamic checkpoints regulating T cell exhaustion in the immune microenvironment [**?**]. Moreover, MCs form an interactive network with the PD-1/PD-L1 axis through PI3K/AKT and calcium signaling pathway activation. In the context of anti-PD-1 therapy, this network transforms their function from releasing immunosuppressive factors IL-10 and TGF-β to promoting anti-tumor responses, ultimately establishing MCs as central hubs of dual-track immunity that comprehensively enhance ICI therapeutic efficacy in breast cancer (Figure 4 [Figure 4: see original paper]).

Note: ICI = immune checkpoint inhibitor, MHC-II = major histocompatibility complex class II molecules, CD80/CD86/CD40 = co-stimulatory molecules,

CCL2/5 = chemokine ligand 2/5, Granzyme B/C = granzymes B/C, STAT4 = signal transducer and activator of transcription 4, ERK = extracellular signal-regulated kinase, MSK = mitogen- and stress-activated protein kinase, CREB = cAMP-response element binding protein.

Figure 4 [Figure 4: see original paper] Anti-tumor molecular mechanisms of mast cells

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5 Heterogeneity of Dual MC Functions Across Breast Cancer Subtypes

5.1 Luminal Subtypes

In Luminal subtypes (particularly Luminal B), MC pro-tumor effects are dominated by hormone receptor signaling. Estrogen (E2) activates estrogen receptor α (ERα) on tumor cells, upregulating intercellular cell adhesion molecule-1 (ICAM-1) and chemokines that recruit MCs to the TME [**?**]. MCs themselves express ER and can be directly activated by E2 to release pro-inflammatory mediators, forming a positive feedback loop. These mediators drive malignant progression through a paracrine-immunomodulatory axis: MCs secrete CCL2/CCL5 to recruit TAMs and Treg cells, and release TGF-β to suppress CD8+ T cell function—an effect amplified by high HER2 (ERBB2) expression in Luminal B [**?**, **?**]. This suggests that dual blockade strategies combining endocrine therapy (e.g., CDK4/6 inhibitors) with MC-targeted agents may simultaneously reverse hormone-dependent and immunosuppressive resistance. Additionally, MC degranulation activates the Notch signaling pathway through Jagged1 ligand, inducing cancer stemness genes sex determining region Y-box 2 (SOX2) and aldehyde dehydrogenase 1 (ALDH1), thereby enhancing mammosphere formation capacity and metastatic potential [**?**]. MCs may also maintain cancer cell survival through the heat shock protein 70 (HSP70)-myelocytomatosis oncogene (Myc) axis [**?**]. Persistent MC-mediated Notch pathway activation can impair tamoxifen response, while HSP70 overexpression promotes chemotherapy resistance. In Luminal B, dysregulated ER/HER2 crosstalk signals combined with high proliferative pressure synergistically exacerbate these mechanisms, leading to greater aggressiveness. Although Luminal A generally has better prognosis, MC infiltration can still enhance invasiveness. However, the immune system is more active in Luminal A TME compared to Luminal B TME [**?**], which may partially offset the tumor-promoting effects of MCs.

5.2 HER2-Positive Subtype

In HER2-positive breast cancer, MC interactions with the HER2 signaling pathway occur through microenvironment-mediated bidirectional regulation. HER2 amplification activates downstream PI3K/AKT and STAT3 pathways, upregulating CCL2 and adhesion molecule expression to promote MC infiltration into

the TME [?]. Infiltrated MCs reciprocally trans-activate tumor cell STAT3 signaling through IL-6 and IL-13 release, forming a positive feedback loop that further amplifies HER2 pathway activity. Simultaneously, MC-secreted TNF-α and SCF bind to the c-Kit receptor on cancer cells, activating the PI3K/AKT/mammalian target of rapamycin (mTOR) axis and inducing HER2 heterogeneity, which enhances tumor stemness factors ALDH1 and mammosphere formation [?, ?]. This interaction directly contributes to targeted therapy resistance by recruiting MDSCs and Treg cells that inhibit NK cell-mediated antibody-dependent cell-mediated cytotoxicity (ADCC)—the core mechanism of trastuzumab action [?, ?]. Sustained MC-mediated PI3K/AKT activation counteracts HER2 inhibitor blockade, rendering trastuzumab ineffective. Clinical reports show that ericalyxin B (Eri B) can reverse HER2 resistance by inhibiting MC transforming growth factor-β-activated kinase 1 (TAK1)/NF- B signaling and blocking IL-6/TNF-α release, thereby disrupting the STAT3-PI3K/AKT-Notch resistance axis and providing a molecular basis for overcoming HER2 resistance [?].

5.3 Triple-Negative Breast Cancer Subtype

The prognostic significance of MC infiltration in TNBC presents significant contradictions, reflecting the complexity of MC functional heterogeneity and microenvironmental regulation. Studies have shown that activated MCs expressing high levels of CD117 and tryptase correlate with poor prognosis in TNBC, likely by promoting cancer stem cell properties and expressing immunosuppressive molecules PD-L2 and galectin-9 (Gal-9) [?, ?]. PD-L2 directly inhibits T cell proliferation and anti-tumor cytokine secretion by binding to PD-1 on CD8+ T cells, while Gal-9 induces T cell exhaustion by binding to the T cell immunoglobulin and mucin domain-containing protein 3 (TIM-3) receptor, suppressing antitumor function [?]. MC degranulation releases pre-stored colony-stimulating factor 1 (CSF1), driving monocyte differentiation into macrophages with a unique polarization phenotype [?]. This process involves epigenetic reprogramming that induces macrophage expression of secondary immune checkpoints PD-L1/PD-L2, forming a cascade inhibition network. In contrast, quiescent MCs (with low activation marker expression) correlate with better prognosis [?], possibly by inhibiting tumor cell migration. However, the TNBC microenvironment exhibits high IL-6 and TNF-α expression, which can synergistically enhance MC sensitivity to IgE, amplifying the risk of allergic reactions with MC-targeted therapy. Sodium cromoglycate, a mast cell stabilizer that can reverse immune resistance and inhibit tryptase release by stabilizing MC membranes, may aggravate the inherent Th2 inflammatory tendency in TNBC patients. Studies have proposed that combining sodium cromoglycate with H1 receptor antagonists may block histamine' s pro-inflammatory effects and balance Th1/Th2 responses to ensure MCs exert positive effects in the TME [?, ?]. Current evidence suggests that the safety concerns of MC-targeted therapy fundamentally result from interactions between the highly inflammatory microenvironment and MC functional plasticity. The paradoxical nature of MCs in TNBC is evident: they may reduce

inflammatory infiltration, yet excessive functional suppression could weaken immune surveillance.

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6 Summary and Outlook

MC functions in the breast cancer TME exhibit high plasticity and duality, with their effects determined by microenvironmental signals, intrinsic heterogeneity, and breast cancer subtype characteristics. MCs drive angiogenesis, invasion, metastasis, and immunosuppressive microenvironment formation by releasing pro-angiogenic factors (VEGF/bFGF), proteases (tryptase/chymase), and immunosuppressive mediators (IL-10/TGF-β/PGE2/PD-L1). Conversely, MCs can directly kill tumor cells through granzyme C release, synergize with DCs to activate Th1 immune responses, and particularly enhance ICI efficacy via apMCs. Regarding subtype-specific heterogeneity: in Luminal B subtypes, MCs are dominated by hormone signaling that promotes Treg recruitment and therapy resistance; in HER2+ subtypes, MCs form bidirectional positive feedback with the HER2 pathway to induce targeted therapy resistance; in TNBC, MCs present contradictions where activated MCs associate with poor prognosis, while quiescent MCs and the critical apMC subset correlate with better prognosis and significantly enhanced ICI efficacy. Therapeutic strategies targeting MCs require precise distinction between pro-tumor and anti-tumor phenotypes, focusing on inhibiting pro-tumor pathways (e.g., TGF-β/tryptase-PAR-2 axis) or activating apMCs combined with ICI. This approach offers new directions for overcoming drug resistance and improving immunotherapeutic efficacy, particularly in TNBC and refractory breast cancer, representing a highly promising strategy.

Current MC-targeted therapeutics such as imatinib, a c-Kit inhibitor, have shown that combination with anti-PD-1 antibodies can induce MC depletion and complete tumor regression [**?**]. Short-term imatinib application effectively enhances anti-tumor efficacy, while prolonged use improves tumor vascular normalization [**?**], though its application in breast cancer remains unexplored. However, the high dynamicity and complexity of MCs in the breast cancer TME pose significant challenges for targeting strategies regarding specificity and timing. Although apMCs demonstrate therapeutic potential, current MC cell sorting technology relies on CD117+/Fc RI+/HLA-DR+ combined markers [**?**], where HLA-DR is also expressed on other immune cells such as DCs, highlighting the lack of MC-specific surface markers. This limitation underscores the practical value of developing integrated in situ fixation and single-cell sequencing technologies. Moreover, the inherent sensitizing properties of MCs necessitate balancing efficacy and safety in future research through the development of TME-responsive drug delivery systems that enrich drugs locally within tumors to enhance anti-tumor effects while avoiding MC-mediated systemic allergic risks.

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Conflict of Interest: The authors declare no conflicts of interest.

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