



REVIEW

Understanding the mechanisms underlying obesity in remodeling the breast tumor immune microenvironment: from the perspective of inflammation

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ABSTRACT

Obesity is a well-known modifiable risk factor for breast cancer and is considered a poor prognostic factor in pre- and post-menopausal women. While the systemic effects of obesity have been extensively studied, less is known about the mechanisms underlying obesity-associated cancer risk and the local consequences of obesity. Thus, obesity-induced inflammation has become the focus of research interest. Biologically, the development of cancer involves a complex interaction with numerous components. As the tumor immune microenvironment changes due to obesity-triggered inflammation, an increase in infiltration occurs for proinflammatory cytokines and adipokines, as well as adipocytes, immune cells, and tumor cells in the expanded adipose tissue. Complicated cellular-molecular crosstalk networks change critical pathways, mediate metabolic and immune function reprogramming, and have a significant role in tumor metastasis, proliferation, resistance, angiogenesis, and tumorigenesis. This review summarizes recent research findings on how inflammatory mediators in the *in situ* tumor microenvironment regulate the occurrence and development of breast cancer in the context of obesity. We analyzed the heterogeneity and potential mechanisms of the breast cancer immune microenvironment from the perspective of inflammation to provide a reference for the clinical transformation of precision targeted cancer therapy.

KEYWORDS

Breast cancer; obesity; inflammatory mediator; tumor microenvironment; metabolism

Introduction

Cancer accounts for 21% of all deaths, making it a major public health problem worldwide. Breast cancer (BC) is the most common malignancy, the incidence of which is increasing. Specifically, BC comprised approximately one-third of newly-diagnosed tumors among women in 2022^{1,2}. BC, which is characterized by excessive epithelial cell proliferation, is a highly heterogeneous and multifactorial disease with a genetic predisposition, associated metabolic disorders, and known environmental factors^{3,4}. It is commonly acknowledged that the tumor microenvironment (TME) is critically involved in cancer initiation, development, and response to therapies^{5,6}.

The TME is a heterogeneous and dynamic cellular milieu composed of resident and infiltrating cells and molecules^{7,8}. Collective evidence has revealed the importance of cellular and molecular interaction networks within the TME for cancer cell survival⁹, and recent studies have focused on elucidating the mechanisms by which stromal inflammatory mediators secreted by TME components influence tumor progression.

As shown in **Figure 1**, the biological properties of tumor cells are inextricably regulated by dynamic shifts in systemic metabolic status due to intimate interactions between tumor cells and their surroundings. Obesity is a chronic metabolic disease that is defined by the accumulation and reprogramming of adipose tissue. Extensive studies have reported a correlation between obesity and breast tumor-related events, such as poor survival, therapy resistance, recurrence, and metastasis¹⁰⁻¹⁹; however, the underlying mechanisms have not been established. Notably, obese patients usually have impaired inflammatory responses and immune regulation. Moreover, a correlation exists between body mass index (BMI) and the proinflammatory state of breast tissue ($P = 0.004$)²⁰, which has a significant role in worsening the prognosis²¹⁻²³. Inflammation is one of the hallmarks of carcinogenesis, and

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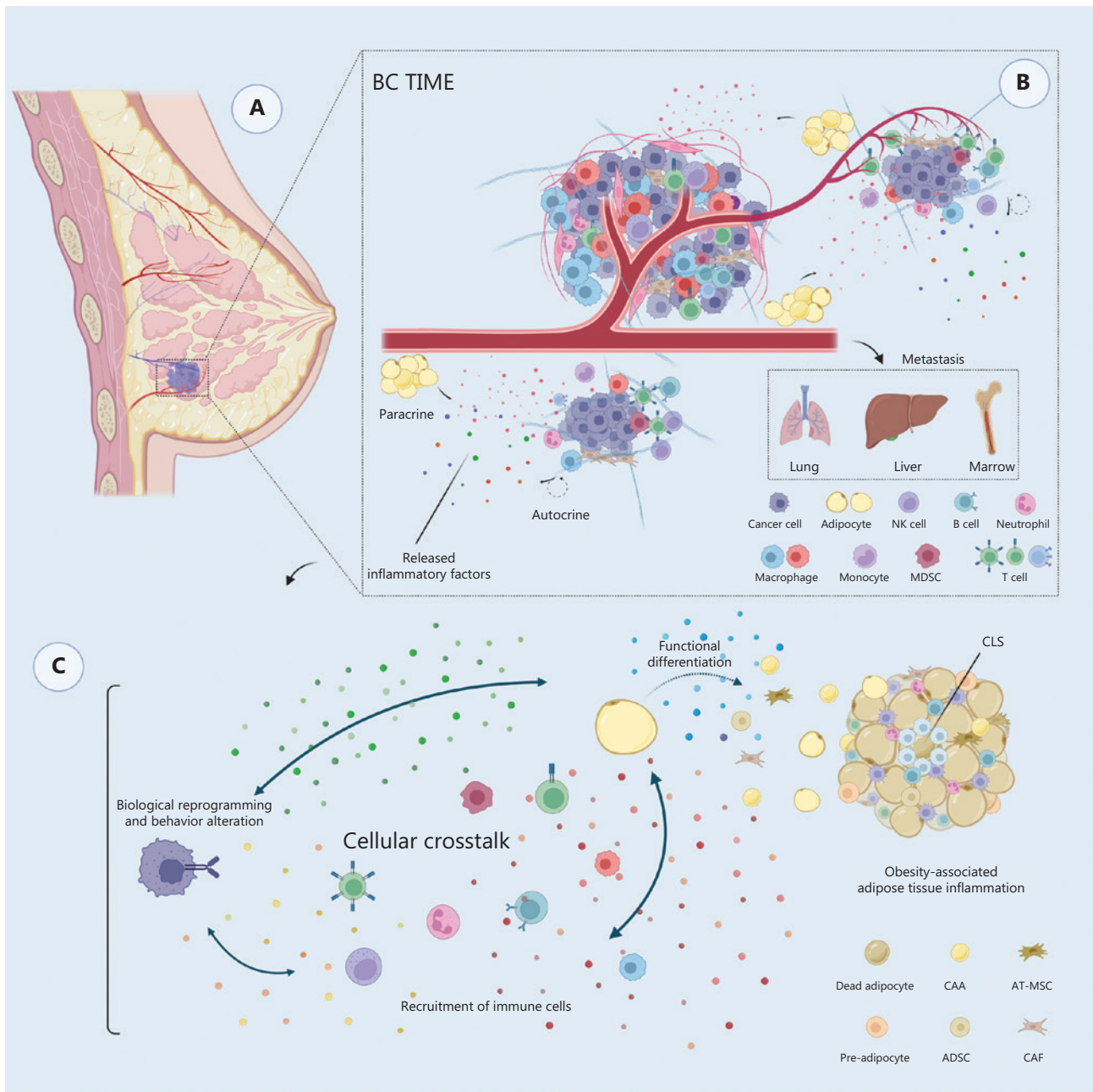


Figure 1 Components and interactions of the BC TME containing adipocytes. (A) The mammary gland is mainly composed of acini and lobules. In the breast, epithelial cells infiltrate around adipose tissue, a unique cell group that maintains the breast morphology. (B) Composition of the TME, including both the physical and biochemical components in the stroma. (C) Schematic representation of interactions between the obesity-associated inflammatory microenvironment and the BC TME. Cellular crosstalk between cancer cells and stromal cell populations leads to various pathologic hallmarks of BC. TIME, tumor immune microenvironment; NK cell, natural killer cell; MDSC, myeloid-derived suppressor cell; CLC, crown-like structure; CAA, cancer-associated adipocyte; AT-MSC, adipose tissue-derived mesenchymal stem cell; ADSC, adipose-derived stem cell; CAF, cancer-associated fibroblast.

researchers have revealed that an inflammatory milieu could favor BC initiation and invasiveness^{24,25}. Obesity stimulates adipose tissue and BC cells (BCCs) to release inflammatory

mediators, predisposing the BCCs to a proinflammatory state, driving oxidative stress, and creating paracrine and autocrine feedback loops²⁶. In summary, the obese environment creates

a distinctive inflammatory milieu in adipose tissue that favors BC initiation, primary growth, invasion, and metastatic progression in conjunction with systemic endocrine alterations.

Tumor progression is typically orchestrated by crosstalk between the tumor and stroma²⁷. The TME in patients with BC is dominated by stromal cells, which actively participate in tumorigenic malignant transformation^{5,12}. Breast ductal epithelial cells are immersed in an adipose environment containing plentiful, specialized adipocytes^{29,30}. The intimate bidirectional relationship between BCCs and para-cancerous adipocytes has been verified^{31,32}. In addition to being an energy resource, adipose tissue is a bioactive organ associated with endocrine, metabolic, and immune systems that regulate systemic energy and metabolic homeostasis, as well as contribute to the composition of the extracellular matrix (ECM) through a complex signaling network^{33,34}. Adipocytes secrete numerous soluble inflammatory mediators that bind to cancer cell receptors and affect BCCs via paracrine signaling pathways^{35,36}. Preclinical models have linked these secreted factors in primary BC to reduced differentiation and poor clinical outcomes^{37,38}. Moreover, adipose tissue is composed of heterogeneous cells, such as adipose-derived stem cells (ADSCs), cancer-associated adipocytes (CAAs), and tumor-associated macrophages (TAMs), that are reprogrammed to exhibit different molecular and cellular characteristics during BC initiation and progression, and increase cancer cell proliferation and invasion capacities by producing inflammatory mediators^{39,40}. Defining these unique differences in adipose components might contribute to a better understanding of how the immunosuppressive BC TME arises.

The mechanisms underlying obesity and inflammation influencing BC are largely unknown. Adipose tissue is an essential modulator of BC biology. Understanding how the obesity-associated *in situ* breast inflammatory microenvironment controls cancer cell behavior and identifying the regulatory elements involved could aid in developing prognostic or therapeutic targets.

Tumor stemness and carcinogenesis in the obese inflammatory microenvironment

Obesity increases the BC incidence, particularly for postmenopausal women^{41,42} (Figure 2). The risk of breast tumor malignant progression may be accelerated by alterations in the

mammary tissue prior to tumor formation^{40,43}. BC emerges due to complicated interactions between the environment and genetics that modify the immune and inflammatory systems to promote carcinogenesis.

Tumorigenesis

Inflammation of white adipose tissue (WAT) is correlated with higher estrogen and aromatase gene expression, both of which are significant risk factors for BC in obese postmenopausal women. Martínez-Chacón et al.³⁸ reported that IL-10 inhibits aromatase gene expression in mesenchymal stem cells (MSCs) and ADSCs by suppressing TNF- α -stimulated ERK1/2 activation. Increased adiposity caused by ovarian hormone deficiency in ovariectomized mice results in enhanced expression of aromatase in mammary adipose tissue mediated by decreased local IL-10. Similarly, Alhallak et al.⁴⁴ reported that compared to normal weight women, IL-10 and FOXP3+ T regulatory levels in breast adipose tissue of obese premenopausal women were upregulated along with the expression of tumor suppressive markers in breast tissue. *In vitro* application of IL-10 was shown to promote apoptosis and inhibit proliferation in the mammary epithelial cell lines, MCF10A and HMEC. In summary, IL-10 may act as a potential protective mediator against BC; however, the current evidence is insufficient and additional research is warranted. Furthermore, the above-cited studies revealed a difference in obesity-associated oncogenesis between pre-menopausal and post-menopausal women, which may reflect hormone levels.

Another study showed that CCL2 augments estrogen production and cancer risk by activating the aromatase promoter, pI.4, via the ERK1/2 pathway. The mammary fat pads of animals with weight gain have significantly higher amounts of IL-6, CCL2, and leptin, which are positively linked with mammary aromatase reporter activity in experiments with human primary breast adipose stem cells (ASCs) and mouse mammary adipose explants⁴⁵. Additionally, local estrogen biosynthesis via aromatase and inflammation are linked to COX-2-dependent PGE2 production in obese breast tissue. Gonçalves et al.⁴⁶ reported that an obesogenic diet augments proinflammatory mediators (CCL2, IL-6, COX-2, and PGE2) in breast tissue, along with the formation of crown-like structures of the breast (CLS-B) and upregulation of local aromatase and estrogen, which accelerate COX-2-dependent breast tumor formation.

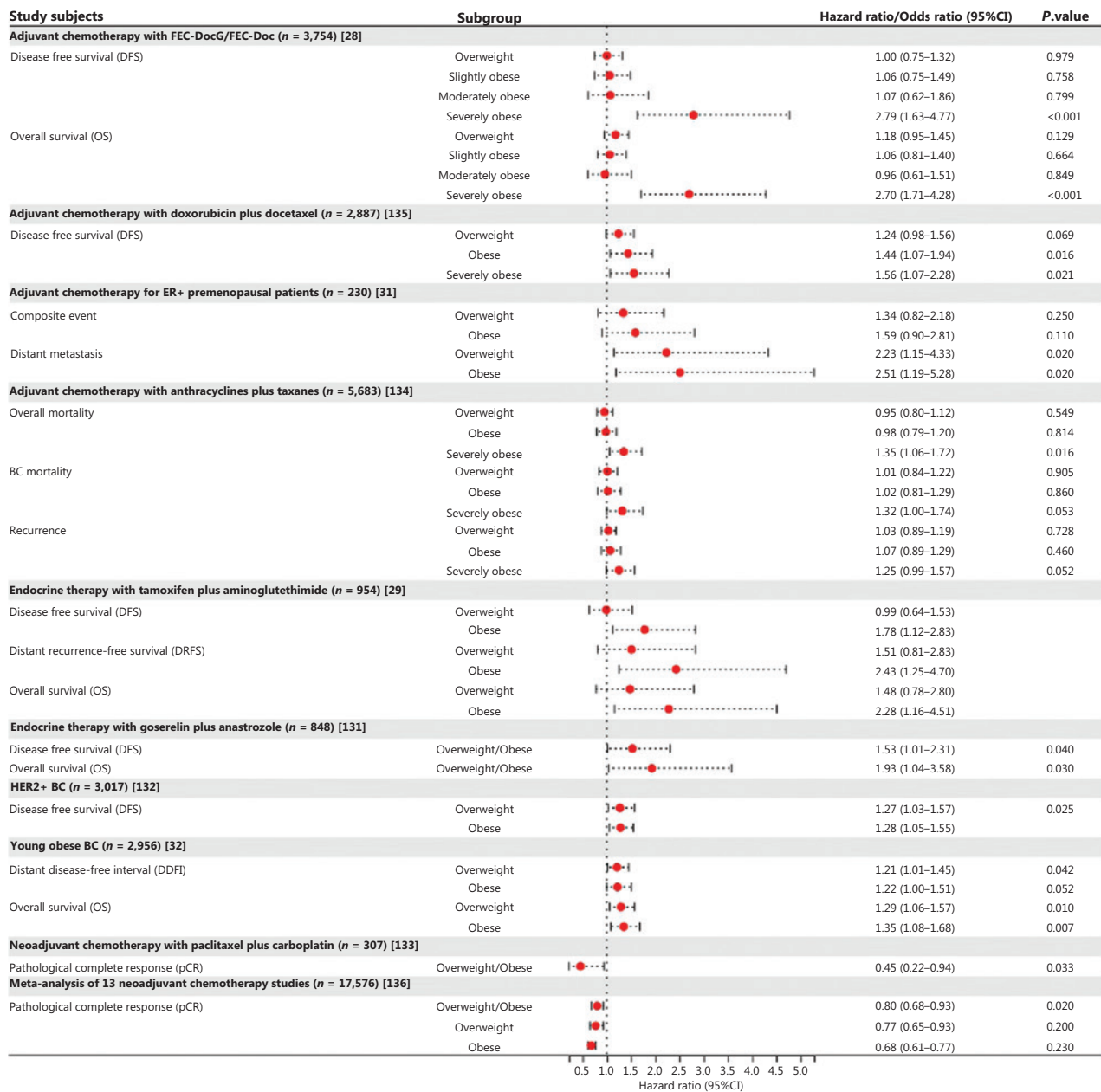


Figure 2 Forest plot of hazard or odds ratio for clinical characteristics in each subgroup from different studies. Each subgroup used the underweight/normal weight group as a reference. FEC-DocG, 5-fluorouracil, epirubicin, cyclophosphamide - docetaxel, gemcitabine; FEC-Doc, 5-fluorouracil, epirubicin, cyclophosphamide - docetaxel; CI, confidence interval. According to the WHO criteria, patients are classified as underweight/normal weight (BMI < 25 kg/m²), overweight (BMI = 25–29.9 kg/m²), slightly obese (BMI = 30–34.9 kg/m²), moderately obese (BMI = 35.0–39.9 kg/m²), and severely obese (BMI ≥ 40.0 kg/m²).

Other inflammatory mediators associated with obesity that may contribute to an increased risk of BC are also of concern. Human triple-negative BC (TNBC)-derived conditioned media increases the expression of the CAA-related cytokines (CCL2, CCL5, IL-1β, and IL-6), as well

as the immune inflammatory regulators, COX-2, HIF-1α, VEGF-α, and PD-L1 in ADSCs during adiposity. The epithelial-mesenchymal transition (EMT) biomarker, Snail, and activation of Smad2 and NF-κB are also correlated with the CAA phenotype, which in turn has a role in

tumorigenesis⁴⁷. Tumor-bearing breast adipose tissue has a distinct physiologic state compared with tumor-free breasts, and the capacity to secrete more IL-8, differentially express genes associated with inflammation and the integrin and Wnt signaling pathways, thereby contributing to tumorigenesis²⁷. Roubert et al.⁴⁸ showed that BMI is positively correlated with the release of IL-1, IL-6, and TNF- α , which stimulates Wnt signaling in mammary tissue and promotes BC⁴⁸. Furthermore, reduced breast epithelial tumor suppressor TGF- β 1 activity and elevated TGF- β 1 within the ECM of obese mammary tissue *in vivo* enhance BC risk, possibly due to interactions with decorin expressed on macrophages surrounding the ducts and lobules in obese breast tissue⁴⁹.

Tumor cell stemness

Some stem or progenitor cell types may increase the probability of developing BC⁵⁰. One study demonstrated that visfatin induces monocyte M2 differentiation *via* ERK/CXCL1 and enhances BCC tumorsphere formation and stemness⁵¹. In addition, when co-culturing human-derived adipocytes with established and primary BCCs, the adipocytes secrete more IL-6 to promote Src activation, thus leading to upregulation of Sox2, c-Myc, and Nanog, which results in the emergence of tumor stem cell traits⁵². As demonstrated by Tiwari et al.⁵³, obesity induces a pro-inflammatory metabolic activation phenotype in mammary adipose tissue macrophages *in vivo*, leading to the secretion of IL-6 in an NADPH oxidase 2-dependent manner and promotes stem-like features to alter the niche and support tumor formation *via* glycoprotein 130 signaling in TNBC cells. ADSCs exhibit tropisms similar to MCF-7 cells, in which secreted macrophage inflammatory protein (MIP)-1 δ and MIP-3 α induce tumorsphere formation *in vitro* and promote tumorigenicity *in vivo*⁵⁴. In addition, adipokines may have an important role in forming stem characteristics. Avtanski et al.⁵⁵ showed that resistin induces MCF-7 and MDA-MB-231 cells to acquire cancer stem cell (CSC)-like properties. The adipokine, adipisin, promotes proliferation and CSC-like characteristics in xenograft models, suggesting that adipisin contributes to the TME and CSC niche in breast malignancies⁵⁶. A-FABP released from adipose tissue promotes tumor stemness by activating the IL-6/STAT3/ALDH1 pathway⁵⁷. Mishra et al.⁵⁸ also showed that leptin promotes BCC stemness, probably through the induction of TGF- β 1 expression and secretion.

Inflammatory mediators from expanded adipose tissue affect BC growth and survival

In addition to the roles in immune regulation and inflammatory responses, obesity-derived inflammatory mediators also facilitate BCC growth and survival. In fact, adipokines may be involved in mediating this effect. Leptin stimulates the proliferation and viability of both ER-positive and TNBC cells, while also promoting anti-proliferative, cytotoxic, and pro-apoptotic effects in MCF-7 cells, similar to TNF- α and IFN- γ ⁵⁹. Accordingly, inflammatory mediators may affect diverse molecular subtypes of BC *via* different mechanisms. There is also evidence that leptin treatment of MCF10A cells leads to increased survival and reduces apoptosis associated with FAK/AKT phosphorylation⁶⁰. Visfatin is an adipokine, the serum levels of which are elevated in various cancers⁶¹. NAD generated by extracellular visfatin increases SIRT1 activity and p53 deacetylation, which induces BCC proliferation⁶². Visfatin-mediated proliferation of MCF-7 and MDA-MB-231 cells is related to the ERK1/2 and AKT signaling pathways⁶³. Additionally, type I IFNs promote aromatase synthesis in adipose tissue surrounding BC and recruit the HIF1 α -IFI16/204-PRMT2 complex to the aromatase promoter, PI.3/PII, which amplifies E2-dependent BC proliferation⁶⁴.

Chemokines maintain an ability to induce targeted chemotaxis in effector cells, and the role of chemokines in promoting tumor proliferation has gained increased attention. In a xenograft model, CCL2-induced inflammation dramatically increases tumor development and facilitates the establishment of a desmoplastic stroma in a xenograft model by early recruitment of macrophages and CAFs into the TME. Fibrocytes may be a potential target inside the TME to minimize tumor fibrosis and improve the treatment response in obese BC patients⁶⁵. Kim et al.⁶⁶ reported significant IL-6 staining in fibroblast-like cells within the peritumoral region, in addition to a positive correlation with CAF markers, thus implying that IL6-positive fibroblast-like cells may originate from pre-adipocytes and mature adipocytes.

Chemokines mediate tumor resistance by participating in the formation of *in situ* regional fibrosis, which in turn leads to tumor growth. Xenograft-bearing mice fed a high-fat diet (HFD) exhibit increased expression of IL-6 and TNF- α to sustain the local chronic inflammatory microenvironment and favor M1 macrophages, which together with nicotine increase

macrophage infiltration and anti-inflammatory cytokines, such as IL-10, IL-13, and IL-4, promote BC growth and invasive behaviors⁶⁷. IL-6 and CXCL1/2/3 are increased and MCP-2 is decreased in human BC-conditioned media, and this effect correlates with tumor stage and histologic grade⁶⁸. The inflammation-related genes, IL6, Ptx3, IL33, and Timp1, are upregulated after 3T3-L1 adipocytes are co-cultured with BCCs, thus promoting proliferation in ER-positive BCCs⁶⁹. Obesity-triggered chemokines are involved in tumor growth; however, there is a lack of in-depth studies with respect to the specific underlying mechanisms.

ADSCs are an important member of the adipose microenvironment. Crosstalk between the secretome and TME may have a role in tumor growth. ADSCs expressing CXCR4 are recruited by SDF-1 α (CXCL12) secreted from chemoresidual TNBC cells. These ADSCs then initiate signaling to drive tumor cell proliferation by secreting FGF2 and activating ERK⁷⁰. ADSC-secreted CXCL5 is a key factor in promoting the proliferation of MCF-7 and MDA-MB-231 cells⁷¹. Another study showed that ADSCs facilitate the growth of MCF-7 and ZR-75-30 cells *in vivo* by secreting the pro-angiogenic cytokines, CXCL1 and IL-8, but have a limited effect on MDA-MB-231 cells⁷². Furthermore, co-injection of c-Kit⁺ ADSCs with 4T1 or endothelial progenitor cells *in vivo* elevate IL-3 and SDF-1 levels and increase tumor volume⁷³. These results may provide a foundation for inhibiting ADSCs or the secretome in the clinical setting.

Obesity-associated inflammation promotes tumor angiogenesis

Angiogenesis is of great significance for tumor development because blood vessels in the TME supply tumor cells with nutrients and oxygen⁷⁴. Tumor cells have been shown to attract bone marrow-derived vascular endothelial progenitor cells (BM-EPCs) and promote angiogenesis *via* the VEGF/HIF-1 α pathway⁶. Pro-inflammatory mediators also maintain angiogenesis and tumor progression, regardless of VEGF blockade⁷⁵⁻⁷⁷. Many of these variables are also increased in obese patients, thus creating a complex microenvironment where cytokines, chemokines, and adipokines are released to cause inflammation and recruit additional pro-inflammatory and pro-angiogenesis mediators⁷⁸⁻⁸⁰. Numerous studies have reported correlations between obesity and enhanced tumor angiogenesis, highlighting the importance of angiogenesis for

the progression of obesity-driven BC^{81,82}. To suppress tumor angiogenesis, several anti-angiogenic agents have been developed, which unfortunately have not yielded the desired results in clinical trials⁸³.

One of the most pressing issues in the effort to improve therapies is how to overcome resistance to anti-angiogenic drugs in cancer patients. Using a zebrafish model of metastasis, Rodriguez et al.⁸⁴ showed that IL-8 generated by breast adipocytes might synergize with LFA-1, integrin, CCL5, or CCL2 to transform the BC microenvironment into a pro-inflammatory and pro-angiogenic state, while inducing resistance against anti-VEGF treatment in ER-positive BCCs. Incio et al.⁸⁵ reported that *in vivo* IL-6 inhibition and FGF-2 adjustment eliminate obesity-induced resistance to anti-VEGF therapy by impacting tumor cell growth, restoring tumor vasculature, alleviating hypoxia, and diminishing immunosuppression. Hsieh et al.⁸⁶ also proposed that IL-8 improves the pro-angiogenic effects of breast adipocytes.

VEGF-A promotes neovascularization, increases vascular permeability, and is closely related to angiogenesis. The obesity-associated inflammatory cytokines, TNF- α , INF- γ , and leptin, increase VEGF-A levels and affect angiogenesis in MDA-MB-231 cells⁵⁹. Elevated IL-6 secreted by adipocytes co-cultured with cancer cells promotes angiogenesis *via* upregulation of STAT3 and VEGF⁵². Moreover, c-Kit⁺ ASCs also improve VEGF levels and vascular formation⁷³.

In addition to directly promoting VEGF-A expression, several potential mechanisms may also mediate tumor angiogenesis. Kolb et al.⁸⁷ reported that obesity increases the number of tumor-infiltrating macrophages with activated NLRP4 inflammasomes and boosts IL-1 β production, thus promoting angiogenesis and cancer progression by upregulating ANGPTL4 expression *via* NF- κ B and MAPK activation. Indeed, targeting ANGPTL4 separately or in conjunction with anti-VEGF treatment may be a more effective strategy for treating obese patients with BC. Another study showed that a pro-inflammatory setting with elevated IL-6 and IL-12 expression and upregulated stress-induced pp38 MAPK and pERK1/2 encourages BC angiogenesis in HFD xenografts⁶⁷. Moreover, WAT-derived GM-CSF and MMP9 promote immunosuppression and intratumor vascularization⁸⁸.

Inflammatory mediators also promote tumor angiogenesis by affecting the activity and function of vascular endothelial cells. Wang et al.⁷² co-injected human ADSCs and BCCs *in vivo* and demonstrated that ADSCs secrete CXCL1 and IL-8 to increase the migration and tube formation of human

umbilical vein endothelial cells (HUVECs) by signaling *via* the receptors, CXCR1 and CXCR2, which in turn enhance angiogenesis and tumor growth. In addition, paracrine activation of integrin β 1-ERK1/2-HIF1 α -VEGFA signaling by MSCs injected into adipose tissue promote HUVEC proliferation, migration, and angiogenesis⁸⁹. Obesity results in the release of increased inflammatory mediators acting on vascular endothelial cells to promote viability, thereby favoring angiogenesis.

Obesity-induced inflammation transforms the mammary gland into a microenvironment conducive to tumor aggressiveness and metastasis

Metastasis remains the predominant cause of the high mortality rate among BC patients, although the 5-year survival rate has greatly increased over the past few decades¹. Tumor dissemination is a complicated process in which tumor cells escape from the primary site, persist in the peripheral circulation, extravasate to distant sites, and ultimately multiply within the target organs. Several factors, including tumor cell characteristics and the local microenvironment in the target area, may affect metastasis. At present, insights into the underlying mechanisms by which obesity-induced metastasis occurs are largely lacking, yet comprehending the connection between obesity and metastasis is imperative to develop targeted therapies for obese individuals.

Chemokines

Chemokines and chemokine receptors have key roles in TME formation, leukocyte recruitment, angiogenesis, and metastasis, and also mediate interactions between tumor cells and tumor surroundings^{90,91}. Targeting CC-chemokine ligand 5 (CCL5) *in vitro* reverses the enhanced motility of TNBC cells upon co-culturing with human adipocytes. CCL5 is also detectable in TNBC peri-tumoral adipose tissue and correlates with lymph node positivity, distant metastases, and reduced overall survival among patients with TNBC⁹². Adipocytes within breast tissue release increased CCL2 when lipid metabolism is altered. Patients with high expression of atypical chemokine receptor 2 (ACKR2) may bind and internalize CCL2 for intracellular degradation to limit tumor metastasis, thus leading to low recruitment of CCR2+ monocytes along with high recruitment of CCR2+ NK cells⁹³. This result may

provide a biomarker for the clinical management of patients. The interactions between adipokines and chemokines also has an essential role. Wang et al.⁵¹ demonstrated that visfatin-induced M2 differentiation in monocytes *via* CXCL1/ERK phosphorylation enhance BCC viability, migration, and EMT *in vitro* and in orthotopic mouse models. *In vitro* experiments showed that leptin leads to BC bone metastases by stimulating the SDF-1/CXCR4 axis, which has been validated using clinical samples⁹⁴. Moreover, 4T1 cells treated with HFD mouse adipose-conditioned medium exhibit enhanced migration ability through CXCL12 and CCL25, with an overall decrease in immune cell infiltration and activation in tumor sentinel lymph nodes, suggesting a high risk of metastasis and immune escape⁹⁵. In summary, obesity may be a risk factor for chemokines to enhance tumor metastasis and immunity exemptions.

Numerous substances, including chemokines, metabolites, and exosomes, are secreted by CAAs and may contribute to BC malignancy⁹⁶. Human CAA-derived leukemia inhibitory factor (LIF) promotes BCC migration and invasion, elevates the expression of BC-derived CXCL1/2/3/8, and activates ERK1/2 signaling to further drive LIF expression in CAAs *via* NF- κ B/STAT3 transcription. This effect forms a positive feedback loop between adipocytes and BCCs. Targeting LIF in combination with CXCR2 greatly decreases *in vivo* BC lung metastasis⁹⁷. Another study showed that ectopic IL-8 expression in tumor-adjacent adipocytes converted adipocytes into CAAs, with high levels of NF- κ B and NF- κ B targets (leptin/IL-8/IL-1 and an active pre-oncogenic STAT3-dependent EMT phenotype), on BCCs and in orthotopic tumor xenografts in mice. Additionally, inactivating CAAs and blocking the IL-8-dependent pro-carcinogenic effects was shown to be achieved by targeting CXCR1/2 in mammary adipocytes *in vitro*⁹⁸. CAA-derived molecules may promote tumor progression through communication with chemokines secreted by tumor cells.

NF- κ B signaling pathway

The relationship between the NF- κ B signaling pathway and pro-inflammatory mediators has been studied extensively and has been shown to regulate inflammation and cellular immune responses. Microarray data have revealed that co-culture with adipocytes induces migration and pro-inflammatory genes involved in NF- κ B signaling in the MDA-MBA-231 cell line⁹⁹. The expression of obesity-related mediators (SphK1 and S1PR1) is enhanced in metastatic lesions of syngeneic

and spontaneous breast tumor obese mice, along with elevated levels of TNF- α and IL-6. Targeting the SphK1/S1P/S1PR1 axis mediated by lipid metabolism attenuates key pro-inflammatory cytokines and macrophage infiltration as well as obesity-induced tumor progression¹⁰⁰. Treatment with 17 β -estradiol, leptin, IL-6, and TNF- α (ELIT) for obesity-related inflammation also decrease mitochondrial function and increase oxidative stress, aggressiveness, and motility in cell lines with low estrogen receptor beta (ER β) expression¹⁰¹. Consistent with this finding, human and mouse adipocyte-derived conditioned media increase BCC migration and proliferation by activating the PI3K-AKT-mTOR pathway and upregulating the expression of target genes, such as TNF- α , IL-1, and IL-6, suggesting that tumor-derived molecules regulate the TME in addition to the tumor, thereby aggravating diseases¹⁰². Another study indicated that upregulation of IL-6 and TNF- α is disrupted by obesity⁹⁵, indicating that obesity may affect the NF- κ B signaling pathway through different mechanisms, which warrant further study.

In addition to directly affecting tumor cells, the NF- κ B pathway is also involved in adipocyte-mediated tumor progression and metastasis *via* paracrine signaling. The growth and migration of 4T1 cells are stimulated by 3T3-L1 adipocyte-conditioned medium, which could be rescued by inhibiting macrophage chemoattractant protein (MCP-1/CCL2), IL-6, IL-1, and plasminogen activators⁸⁶. Pre-adipocytes upregulates IL-6 secretion and promotes proliferation, migration, and invasion of MCF10DCIS.com cells, which can be attenuated by blocking IL6-mediated cross-linking *in vitro* and in a xenograft tumor model⁶⁶. These results indicated that human adipocyte-derived IL-6 and leptin boost BC proliferation and metastasis, and induce an EMT phenotype *in vitro* by activating PI3K-AKT and IL-6/JAK-STAT3 signaling^{103,104}. Additionally, using a zebrafish model of metastasis, Rodriguez et al.⁸⁴ demonstrated that the release of IL-8 by breast adipocytes might cause neutrophils to adopt a pro-tumorigenic phenotype, which would then promote the dissemination of ER-positive BCCs. In conclusion, the NF- κ B signaling pathway may promote tumor metastasis by affecting tumor cells and adipocytes.

ADSCs

Multipotent ADSCs have attracted extensive attention because of the regenerative properties in plastic surgery; however, these features are also connected to metastasis and tumor

initiation, raising concerns about safety in clinical applications¹⁰⁵. Human ADSC-secreted IL-6 significantly stimulates proliferation, EMT, transmigration, and 3D invasion of human primary normal and tumor epithelial cells¹⁰⁶. Blocking ADSC/Th2-derived IL-4 depleted metastatic ADSCs and elevated the expression of DUSP4 by inhibiting NF- κ B and impairing the RAS/P38-MAPK pathway, thus delaying the proliferative and invasive phenotype of BCCs and driving the transformation of metastatic cells into non-metastatic cells¹⁰⁷. By cross-reacting with the transforming growth factor (TGF)- β /Smad and PI3K/AKT pathways, the paracrine impact of ADSCs promotes EMT of MCF7 cells¹⁰⁸. Moreover, Chang et al.¹⁰⁹ discovered that adipose tissue-derived mesenchymal stem cells (AT-MSCs) obtained from type 2 diabetes mellitus (T2DM) donors differentiate into cancer-associated fibroblasts (CAFs) when co-cultured with BCCs under hypoxic conditions, in turn promoting BCC proliferation and *in vivo* metastasis, as well as the expression of fibroblastic markers, which was associated with TGF β -Smad2/3 signal activation. Understanding the inflammatory characteristics of ADSCs may help develop applications in the clinical setting.

Immunomodulatory factors

Immune cells interact with tumor cells *via* immunomodulatory factors in the TME, which affects tumor behavior and treatment efficiency. A diet-induced obese mouse model showed elevated collagen production and proliferative rates of lung stromal cells, and the upregulated CSF2- and TGF- β 1-induced recruitment and invasion of myeloid cells, as well as an immunosuppressive macrophage phenotype, respectively, which are correlated with pre-metastatic niche formation and lung metastasis of primary mammary tumors¹¹⁰. As a growth factor for hematopoietic and immune cells, granulocyte-macrophage colony stimulating factor (GM-CSF) mobilizes stem cells and causes macrophage/granulocyte differentiation in addition to regulating inflammation and autoimmune disease¹¹¹. Liu et al.¹¹² identified G-CSF and the G-CSF target gene matrix metalloproteinase (MMP) 2 and 9 in CAAs through transcriptomic sequencing. Treatment of TNBC cells with G-CSF enhance EMT, migration, and invasion through activation of STAT3 in cooperation with IL-6 and GM-CSF. TGF- β activates ERK and phosphorylates SMAD4 in obese patients, which allows USP9x to block the binding and mono-ubiquitination of SMAD4, thereby maintaining SMAD4 while promoting TGF- β /SMAD3-mediated

transcription of EMT markers. Free fatty acids (FFAs) further facilitate the process and promote TGF β -dependent cancer invasion and metastasis¹¹³. In addition, Wolfson et al.¹¹⁴ reported that increased TGF- β 1 in the mammary adipose tissue of obese mice activate SMAD3 signaling and inhibit miR-140 transcription, thus preventing miR-140 from targeting SMAD3 for degradation, resulting in the formation of a fibrotic microenvironment that impacts stemness, invasion, and proliferation of ductal epithelial cells. According to Quail et al.¹¹⁵, obesity-produced IL-5 boosts CSF2 expression by IL5R α + monocyte and neutrophil transport to the lungs of mice. In addition, obesity-related pro-metastatic effects can be reversed by blockade of GM-CSF or weight loss. After co-culturing with BC, human-derived WAT-derived ADSCs dramatically upregulate the expression of GM-CSF and MMP9, neutralization of which significantly reduced local and metastatic BC progression *in vivo*. This process is related to reducing macrophages and myeloid-derived suppressor cells (MDSCs) and can be inhibited by metformin, suggesting that proteins may be novel targets for this widely used drug⁸⁸. Among all immune cells present in the BC TME, monocytes or TAMs account for the majority and are correlated with obesity and a poor prognosis in BC patients. Targeting or reversing the differentiation into monocyte-macrophage immunosuppressive phenotypes and the immunoregulatory factor, TGF- β , may have clinical application.

Adipokines

Adipokines mediate tumor development through tumor-stromal interactions in the TME. As a cytokine-like hormone, leptin serves as a bridge between BC and obesity. Knockdown of ObR in BCCs induce a less proliferative and invasive tumor phenotype¹¹⁶. Treatment with leptin induce EMT, migration, and invasion of BCCs and MCF10A cells, which correlate with increased FAK/AKT phosphorylation⁶⁰. Gelsomino et al.¹¹⁷ showed that aromatase inhibitor (AI) anastrozole-resistant MCF-7 BCCs (AnaR) express higher levels of leptin along with AnaR receptors and that targeting leptin signaling reduce growth and viability. Another study showed that leptin reduced cell aggregation and increased cell proliferation, migration, invasion, and EMT of cancer and epithelial cell lines, possibly by inducing TGF- β 1 expression and secretion⁵⁸. MDSCs are known promoters of cancer progression. Obesity-induced inflammation upregulates leptin *in vivo*, which induces the accumulation of excessive MDSCs and further facilitates

spontaneous growth and metastasis by suppressing the activation and function of tumor-reactive T lymphocytes¹¹⁸.

Other types of adipokines also have an important role in tumor invasion and metastasis. Resistin stimulates motility in MCF-7 and MDA-MB-231 cells through cytoskeletal remodeling and EMT reprogramming⁵⁵. A-FABP released from adipose tissue directly targets BCCs and enhances tumor aggressiveness *in vivo* by activating the IL-6/STAT3/ALDH1 pathway⁵⁷. In addition, A-FABP expression in CD11b+F4/80+MHCII-Ly6C- phenotype TAMs facilitates protumor IL-6/STAT3 signaling by regulating the NF κ B/miR-29b pathway, and A-FABP deficiency significantly decreases the growth and spread of breast tumors in transgenic and syngeneic tumor models¹¹⁹. Consequently, adipokines may be a potential target for the precise treatment of BC, but specific mechanisms need to be investigated further.

The impact of obese stroma on tumor cells and exposure to heightened inflammatory mediators present in the TME lead to alterations in the mammary epithelium that possibly predispose women to the developing of more aggressive BC.

Inflammation triggered by obesity makes the breast TME resistant to therapeutic approaches

A significant barrier to treating cancer is the resistance to chemotherapy and molecular-targeted therapies. Despite high response rates to initial therapy, many cancers eventually lose sensitivity to original treatment methods, resulting in metastasis and mortality. The TME is crucial in intrinsic drug resistance pathways¹²⁰, and patients who are obese are more likely to develop treatment resistance^{98,121}. Prior research has demonstrated that peri-tumor adipocytes contribute to the development of a radio-resistant phenotype in BC¹²². A recent study also found adipocytes to actively convert the chemotherapeutic agent daunorubicin into a less effective metabolite¹²³.

Resistance to chemotherapy and endocrine therapy

Tumors adopt various pathways to inhibit chemotherapy efficacy, in which obesity-associated inflammatory pathways may be involved. The anti-proliferative effects of tamoxifen on MCF-7 cells are counteracted by co-culture with mature adipocytes from obese women, which significantly increase

expression of TNF- α and IL-6¹²⁴. Further evidence supports the role of obesity-induced inflammatory responses (IL-6, TNF- α , and leptin) in tamoxifen-acquired BC resistance⁸⁵. Human ADSC-secreted CXCL1 *in vitro* downregulates miR-106a and upregulates ABCG2, a transporter of doxorubicin efflux in TNBC, thus conferring doxorubicin resistance¹²⁵. The inflammatory adipocytokines (leptin, CCL2, IL-1 β , and resistin) secreted by adipocytes and FFAs released by MDA-MB-231 cells confer acquired doxorubicin resistance in BC by generating inflammation and lipid metabolic reprogramming in the TME⁶¹. Mentoer et al.¹²⁶ suggested that obesity-induced resistin inhibits *de novo* fatty acid synthesis and lipolysis in mammary adipose tissue of mice, further aggravating local inflammatory reactions *via* the NF- κ B pathway and promoting TNBC survival together with reduced doxorubicin efficacy in a paracrine manner. In addition, the adipokine, visfatin, enhances cell viability and prevents the reduction of survivin, a well-known candidate for chemoresistance of cancer cells, in TNF α -induced apoptosis and PARP cleavage⁶³.

Resistance to radiotherapy

Radiotherapy is a mainstream BC treatment, and the TME is known to influence radiosensitivity. Inflammation is a crucial aspect of radiotherapy because inflammation can be triggered by released debris and the production of proteins induced by radiotherapy to enhance immune system elimination of cancer cells¹²⁷. Autotaxin (ATX) is mainly secreted by mammary adipocytes in BC; however, as a component of the wound healing response, the ATX-lysophosphatidate (LPA)-inflammatory cycle shields cells against radiation-induced death and facilitates fibrosis¹²⁸. Exposure of rat- and human-derived adipose tissue to γ -radiation produces a significant inflammatory response, and inflammatory cytokines secreted by breast tumors, including IL-1 β , IL-6, IL-10, and TNF- α , stimulate ATX secretion by activating the NF- κ B pathway. This response, in turn, generates LPA and stimulates further activation of NF- κ B, which results in a positive feedback loop that promotes BC growth and metastasis¹²⁹. Meng et al.¹³⁰ confirmed that repeated fractions of radiotherapy activate the above-outlined cycle, further increasing concentrations of VEGF, CXCL10, CCL11, and G-CSF in irradiated fat pads, thereby reducing the efficacy of additional fractions. Moreover, targeting ATX in a syngeneic orthotopic mouse model of BC decreased CCL11, IL-9, IL-12p40, M-CSF, and IFN- γ , which reversed pro-survival signals and radio-resistance in cancer cells. Furthermore,

ATX inhibition is synergistic with irradiation and doxorubicin to decrease tumor growth and the number of Ki67-positive cells¹³¹. Inhibition of the adipose-related ATX pathway restores the pro-inflammatory properties of radiotherapy, and is therefore effective when combined with other therapeutic modalities.

Potential roles of inflammatory mediators in modulating immune responses

In recent years the development of immunotherapies based on immune checkpoint blockade (ICB) has dramatically reshaped the landscape of cancer therapy; however, despite the improved prognosis in a subset of cancer patients using currently-available immunotherapeutics, the response rate among TNBC patients is < 20%^{132,133}, largely owing to the immunosuppressive TME. Therefore, a major focus of research involves discovering and addressing variables that contribute to the immunosuppressive TME. Obesity may be one such variable, with evidence suggesting that obesity perturbs the immune system and allows macrophages and T cells to differentiate into phenotypes that favor tumor growth²². Nevertheless, one study also showed that obese cancer patients have better overall survival, progression-free survival, and response rates after ICB treatment¹³⁴. Accordingly, further study is needed to determine how obesity affects the outcomes of cancer patients receiving immunotherapy.

T and B cells are the main types of lymphocytes and have various biological functions, such as the direct killing of target cells, the production of cytokines and antibodies, and immune regulation. Gibson et al.¹³⁵ reported that obesity increases the concentration of CXCL1 in the mammary TME, drives CXCR2-mediated chemotaxis, and accumulates granulocytic MDSCs (G-MDSCs) to stimulate CD8+ T-cell apoptosis *via* Fas/FasL, leading to immunotherapeutic resistance in obese mice. By increasing intracellular IFN- γ and reducing PD-1 expression, blocking the IL-4 pathway promotes CD8+ T-cell cytotoxicity, thus sensitizing BCCs to anti-cancer therapy and enhancing the immune responses¹⁰⁷. Another study indicated that the expression of leptin, CXCR4, and CCR9 in obese TNBC patients is negatively correlated with CD8+ T-cell infiltration⁹⁵. Furthermore, ADSCs suppress B-cell proliferation, reduce the TNF- α +/IL-10+ B-cell ratio in a contact-dependent manner, and alter the cytokine profile of B cells to an anti-inflammatory profile¹³⁶. IL-6 inhibition reverses the recruitment of immunosuppressive regulatory T cells induced

by anti-VEGF treatment in obese mice, suggesting that IL-6 suppression may augment immunotherapy in the context of obesity⁸⁵. Additionally, pro-tumoral IL-17+ $\gamma\delta$ T cells multiply in obese mouse tumors, exhibit high lipid absorption, and intracellular lipid storage, indicating that metabolic programming regulates the immune cell lineage and function¹³⁷. Moreover, using 4T1 tumor models in the presence or absence of adipocytes, Liu et al.⁹¹ noted that TAA-secreted CCL2 recruits monocytes and macrophages to become immunosuppressive MDSCs and M2 macrophages. Targeting CCL2 *in vivo* increases T-cell infiltration, ameliorates the immunosuppressive TME, and facilitates immunotherapy.

Monocytes and macrophages are involved in innate immunity and have an important role in antigen presentation and immune regulation; however, an increasing number of studies have shown that myeloid cells have a large number of immunosuppressive phenotypes that have an important role in mediating tumor immune escape. Obesity-related M1 macrophages secrete IL-6 *via* a JAK/STAT-dependent pathway to promote PD-L1 expression in TNBC, and telmisartan reverses this process by activating peroxisome proliferator-activated receptor (PPAR- γ) and inhibiting NF- κ B P65, thus highlighting the potential application in adjuvant TNBC immunotherapy¹³⁸. Moreover, AnaR-secreted leptin enhances macrophage motility and induces an M2-like phenotype *via* CXCR4 signaling, highlighting the clinical advantage of targeting the cytokine network in obesity-associated hormone-resistant breast tumors¹¹⁷. Consistent with this finding, loss of ObR reduces macrophage recruitment, resulting in decreased CCL2 in xenograft tumors and co-culture experiments. In addition, the absence of Ob/ObR signaling regulates the immunosuppressive TME, as shown by reduced expression of PD-L1/PD-1/arginase 1 and increased phagocytosis capability in macrophages¹¹⁶. Accordingly, obesity-associated inflammatory signals promote the formation of an immunosuppressive microenvironment and tumor immune escape by inducing macrophage differentiation into a pro-tumor phenotype and increasing immune checkpoint expression.

Discussion and future perspectives

Despite the well-documented association between obesity and cancer, the underlying mechanisms are unclear. Recognition of obesity as a chronic inflammatory condition, however, implies potential roles for inflammatory cytokines in

obesity-associated BC (Figure 3). Nevertheless, there remain many unanswered questions.

To determine the disease extent and develop successful treatments, it is essential to recognize cancer as a complex and interconnected process. The inflammatory and obese microenvironment of BC is not confined to the effects of the adipocyte secretome. Stromal cells in the microenvironment release inflammatory mediators to affect cancer behavior and survival. Similarly, cancer cells also induce changes in surrounding cells *via* the secretome¹³⁹. Interactions among immune cells, cancer cells, adipocytes, the immunome, and the metabolome generate intriguing dynamics and lead to the secretion of important molecules that are likely to be potential subjects for inflammation-targeted therapies in the future (Table 1). Although many studies have identified cells and molecules that may have roles in mediating BC, there has been a lack of continuous observations and cell tracking to distinguish different cell types, determine the specific source of inflammatory molecules, or determine whether other microenvironmental factors are involved. Due to the many molecular BC subtypes, diverse interactions and heterogeneity are displayed⁷², yet this finding seldom receives any notice from researchers. Moreover, different adipocyte subpopulations between pre- and post-menopausal breast tissues likely utilize distinct mechanisms to make neighboring epithelial cells sense activated inflammatory signaling and exhibit diverse responses⁴⁴. In brief, variables that may influence the heterogeneity of the TME warrant consideration.

Tumors grow in a complex microenvironment containing diverse cell types and inflammatory mediators. Beyond the local TME, a systemic inflammatory environment can also influence the disease course by interfering with homeostasis in a variety of tissues across the body. Many studies, however, do not consider *in vivo* inflammation, instead identifying interactions between tumor cells and adipocytes using co-cultivation methods. This approach may overlook the systemic effects of metabolism and immunity and lead to different consequences. Therefore, the complex interplay of inflammatory mediators in the context of an immunocompetent host remains to be explored. Additionally, it is unknown whether any of the current findings can be applied to the microenvironment of human BC; further exploration is needed in more reliable models, such as xenograft mice and organoids.

As a systemic disease, complex interactions occur between obesity and the endocrine and metabolic systems of the body, and the comprehensive effect on the tumor immune microenvironment (TIME) needs to be further explored. Obesity

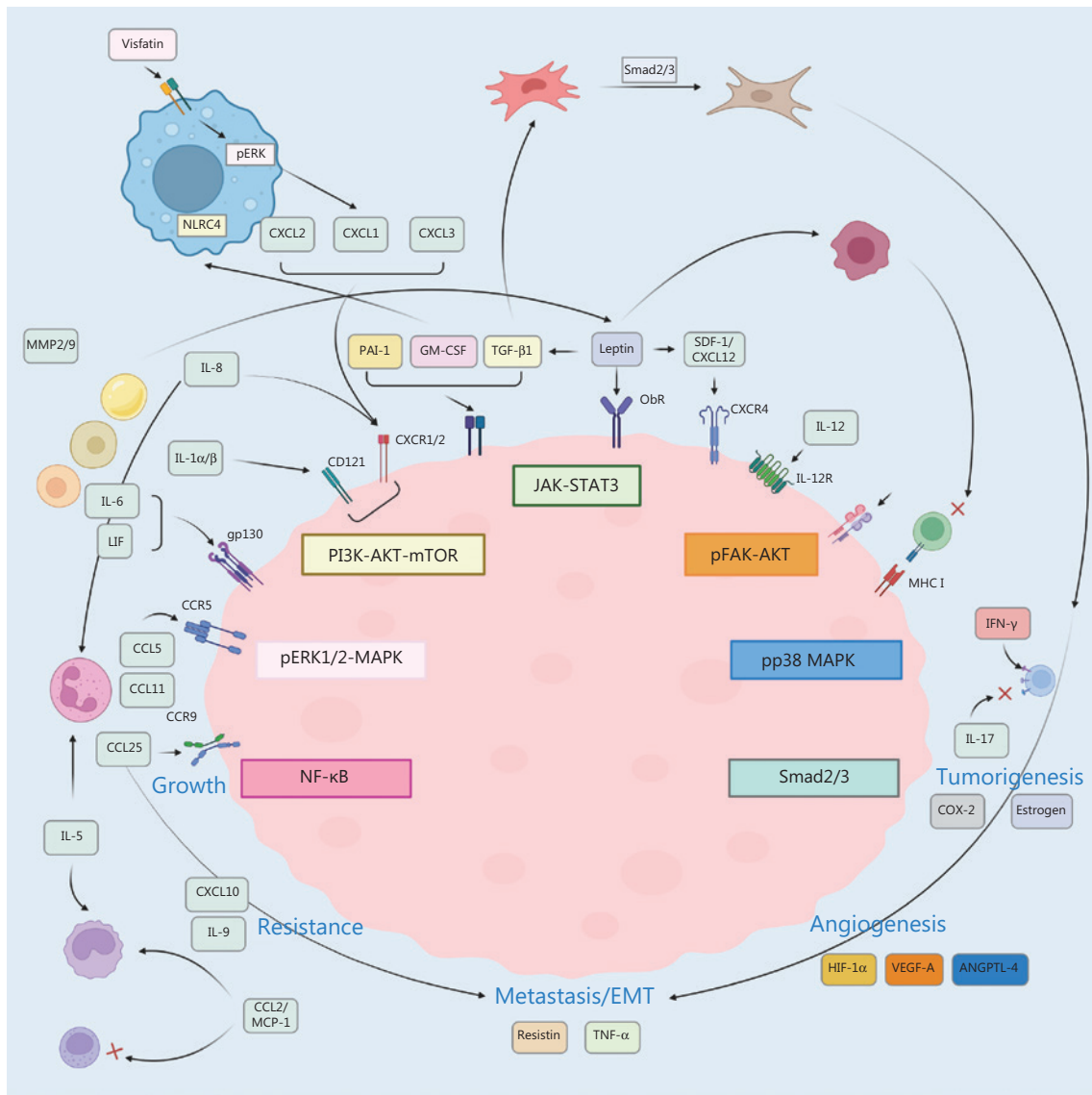


Figure 3 Summarized potential inflammatory pathways that may be involved in obesity-associated TIME. Continuous cell proliferation and differentiation in a microenvironment containing inflammatory cells, growth factors, activated matrices, and DNA-damaged materials are crucial for inflammation to encourage cancer formation. The TIME is the essential condition for differentiation, survival, and metastasis, and inflammatory cells are closely involved in regulating the TIME. The remodeled breast TIME secretes inflammatory mediators that crosstalk with cells by acting on surface receptors, activating inflammation-related signaling pathways, and modifying the behavior of tumor, immune, and stromal cells. In an inflammatory microenvironment, there are three primary stages for tumor formation and development (initiation, promotion, and metastasis). The inflammatory microenvironment involves immune cells, inflammatory cells, and various produced bioactive chemicals, such as $TNF-\alpha$, $IFN-\gamma$, interleukin, and chemokines, which participate in cancer cell tumorigenesis, growth, angiogenesis, metastasis, and resistance to therapeutic approaches.

causes altered glucose metabolism and increases circulating FFAs, which results in hyperinsulinemia and insulin resistance, elevates the secretion of pro-inflammatory cytokines, causes excessive activation of insulin receptors, and promotes tumor proliferation. Insulin resistance often occurs along

with obesity, and like obesity, insulin resistance influences the TIME through inflammatory pathways, such as $IKK-\beta$ or $NLRP3$ ^{140,141}. In addition, Wang et al.¹⁴² suggested that insulin resistance in vascular endothelial cells forms a pro-inflammatory state, showing higher levels of cell adhesion

Table 1 Potential inflammatory targets of BC

	Agent	Inflammatory pathway	Impact on tumor	Reference
Metastasis				
CXCR4	AMD3100	SDF-1/CXCR4	Bone metastasis	94
LIF	EC330	LIF-CXCL1/2/3/8-CXCR2	Migration/invasion; lung metastasis	97
CXCR2	SB225002			
CXCR1/2	Reparixin	IL8-CXCR1/2	Migration/invasion	97,85
S1P	FTY720/fingolimod	SphK1/S1P/S1PR1	Cytokines/macrophage infiltration	100
GLUT	Metformin	GM-CSF/MMP9	Metastasis progression	87
STAT3	Stattic	IL6-STAT3	EMT/migration/invasion	112
Resistance to Therapy				
Autotaxin	GLPG1690	ATX-LPA	Resistance to radiotherapy	131
CCL2	CCL2-binding trap	CCL2-T cell	T-cell infiltration	91
Angiotensin receptor II	Telmisartan	PPAR γ /NF- κ B P65-IL6	PD-L1 expression	138
Angiogenesis				
VEGF	B20-4.1.1	VEGF	Angiogenesis	85
IL-6	/	IL6-Treg	Reverse anti-VEGF-induced Treg recruitment	
ANGPTL4	/	ANGPTL4	Angiogenesis	87
CXCL1/2	SCH527123	CXCL1/8-CXCR1/2	Angiogenesis	72
Tumorigenesis/Stemness				
pERK	PD98059	Visfatin-pERK-CXCL1	EMT/migration/invasion; stemness	51
COX	Aspirin	Inflammatory/angiogenic mediators	Tumorigenesis	86

proteins and neutrophil infiltration, promoting tumor progression. The study suggested that insulin resistance in the TIME is equally heterogeneous; however, additional studies are needed to verify the findings and the roles obesity and insulin resistance have in the inflammatory TIME.

BC exhibits high genotypic and phenotypic diversity, and heterogeneous cell types within the TME exhibit dynamic and tumor-promoting behaviors during cancer progression. Therefore, identifying interactions between individual cells and cytokines, as well as microenvironmental regulators of tumor progression, is essential to develop predictive molecular signatures and more effective treatments. Sophisticated multiomics technologies, such as genomics, proteomics, metabolomics, single-cell omics, and spatial transcriptomics, comprehensively analyze and reflect tumor heterogeneity at the single-cell level. High-throughput data can be used to analyze the spatial structure of the TIME at the level of single-cell

clustering, with far-reaching significance for the realization of precise cancer therapy.

Accordingly, for an integrated understanding of cancer, research into how the systemic environment affects tumor biology is essential. Accurate and efficient analysis of the complex TME and evaluating the meaning of biological targets or biomarkers for clinical applications has been challenging for researchers. Predictive models are data-driven algorithms that combine multiple important outcome-related predictors to assess the prognosis, curative efficacy, and risks of developing a disease based on a variety of mathematical modeling approaches. For example, an integrated analysis of multiple databases from Zhao et al.¹⁴³ identified 10 hub genes associated with the extent of immune cell infiltration into the TIME and patient prognosis. The genes may serve as a risk and survival predictor of BC TIME. By applying mathematical methods to clinical medicine, increasingly accurate predictive

clinical models have been developed to aid patients and clinicians in making decisions.

With the continuous advances in technology, next-generation sequencing, including whole exon and RNA sequencing, has been gradually utilized in clinical practice, thus providing massive data that help us explore biological factors related to the treatment response and prognosis. Moreover, pathologic images of human tumor tissue contain a large amount of information that people cannot fully distinguish and understand. Artificial intelligence can extract complex information from visual data, digitally analyze histologic tumor slices, and infer molecular and genetic changes in tumor tissues to provide a wide range of clinically-relevant applications. For example, researchers recently constructed a simplified mathematical model to predict systemic immune cell connectivity and the dynamics of immune interactions using a high-throughput surface receptor screening method, thus providing a comprehensive view of the human immune system at the single-cell level that may provide opportunities for clinical therapeutic interventions¹⁴⁴. High-throughput mathematical and digital models perform well in elucidating biological processes and identifying key factors of clinical significance, which is a subject that needs future investigation and has profound clinical translational value.

Conclusions

During cancer development, different types of stromal cells establish essential information exchanges with luminal and basal epithelial cells present in the mammary ducts through paracrine signaling or cell-cell communication within the mammary adipose microenvironment. A thorough understanding of this epithelial-stromal interaction might uncover new pathways and mechanisms involved in tumor progression, with an increasing number of studies shifting the targets from the internal communication between cancer cells to the interaction between malignancies and the surroundings. Given the complicated function of the aforementioned obesity-related inflammatory mediators in the TME, addressing the paracrine metabolic reprogramming and immunomodulatory pathways might be an efficient strategy to combat BC. On the premise of clarifying the heterogeneity of the TME, combining cell therapies inhibiting targeted inflammatory molecules with other conventional chemotherapy, immunotherapy, and radiotherapy strategies is a promising direction for treating BC.

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Conflict of interest statement

No potential conflicts of interest are disclosed.

Author contributions

Conceived and designed the analysis: Yingying Xu, Mozhi Wang, and Hengjun Zhang.

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Prepared the figures: Hengjun Zhang and Mozhi Wang.

Wrote the paper: Hengjun Zhang.

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