Heliyon 10 (2024) e35200

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon

Review article

Dissecting the emerging role of cancer-associated adipocyte-derived cytokines in remodeling breast cancer progression

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ARTICLE INFO

Keywords:
Breast cancer
Tumor microenvironment
Cancer-associated adipocytes
Cytokines
Immune regulation

ABSTRACT

Breast cancer has been reported to transcend lung cancer as the most commonly diagnosed cancer in women all over the world. Adipocytes, serving as energy storage and endocrine cells, are the major stromal cells in the breast. Cancer-associated adipocytes (CAAs) are adjacent and dedifferentiated adipocytes located at the invasive front of human breast tumors. Adipocytes can transform into CAA phenotype with morphological and biological changes under the remodeling of breast cancer cells. CAAs play an essential role in breast cancer progression, including remodeling the tumor microenvironment (TME), regulating immunity, and interacting with breast cancer cells. CAAs possess peculiar secretomes and are accordingly capable to promote proliferation, invasiveness, angiogenesis, metastasis, immune escape, and drug resistance of breast cancer cells. There is a complex and coordinated crosstalk among CAAs, immune cells, and breast cancer cells. CAAs can release a variety of cytokines, including IL-6, IL-8, IL-1β, CCL5, CCL2, VEGF, G-CSF, IGF-1, and IGFBP, thereby promoting immune cell recruitment and macrophage polarization, and ultimately stimulating malignant behaviors in breast cancer cells. Here, we aim to provide a comprehensive description of CAA-derived cytokines, including their impact on cancer cell behaviors, immune regulation, breast cancer diagnosis, and treatment. A deeper understanding of CAA performance and interactions with specific TME cell populations will provide better strategies for cancer treatment and breast reconstruction after mastectomy.

1. Introduction

Breast cancer is the most common cancer type and the leading cause of cancer mortality in women. A recent epidemiological survey reported that female breast cancer transcended lung cancer as the most commonly diagnosed cancer worldwide [1]. Breast cancer

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https://doi.org/10.1016/j.heliyon.2024.e35200
Received 10 May 2024; Received in revised form 4 July 2024; Accepted 24 July 2024
Available online 26 July 2024

originates from the terminal duct lobular units of the conducting duct [2]. Based on the anatomical distribution, a fully differentiated breast consists of the breast skin and internal breast structure, which contains glandular tissue and connective tissue [3]. Moreover, the mammary glandular lobes involve lobules and ducts, and the connective segment is composed of fibro-adipose pockets. Typically, the basement membrane, which mainly contains collagen IV, laminin, and fibronectin, separates normal mature adipocytes from epithelial cells, thus limiting the crosstalk between these two cell types [4]. In pace with breast cancer progression, increased genetic and epigenetic instability and remodeled extracellular matrix (ECM) may eventually contribute to the destruction of the basement membrane, which manifests as the epithelial-to-mesenchymal transition (EMT) of cancer cells.

The tumor microenvironment (TME) refers to a complicated, heterogeneous, and spatiotemporally variable ecosystem, which contributes to the biological behaviors and malignant evolutions of tumors. TME contains a wide variety of cell types, including immune cells, adipocytes, pericytes, fibroblasts, vascular endothelial cells, bone marrow mesenchymal stromal cells, and macrophages, as well as ECM proteins. There are also abundant soluble secreted factors promoting tumor angiogenesis, proliferation, invasion, and metastasis together with those cellular components in the TME [5–8]. Breast cancer cells can domesticate TME through paracrine and autocrine, and reprogramed TME in turn further promotes malignant tumor events. Therefore, these characteristics enable TME to be indispensable in breast cancer development, tumor diagnosis, and treatment.

Adipocytes are indispensable in TME in terms of both quantity and function. Adipose tissue as an endocrine and immune organ, contains an intricate network of heterogeneous cell types, including pre-adipocytes, adipocytes, endothelial cells, fibroblasts, leukocytes, and bone marrow-derived macrophages [9,10]. Adipose tissue can be broadly classified into three types: white, beige, and brown adipose tissue. The white adipose tissue (WAT) consists of adipocytes with a large cytoplasmic lipid droplet, serving as the main energy storage compartment [11]. The adipocytes in brown adipose tissue (BAT) are characterized by small droplets of lipids, packed mitochondria, and thermogenesis to maintain body temperature. The morphology and function properties of beige adipose tissue are between those in WAT and BAT. In mammary tumors, white adipocytes make up the majority of the TME and facilitate cancer progression by producing several inflammatory factors, such as interleukin-1 beta (IL-1β), interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), C–C motif chemokine ligand 2 (CCL2), leptin, and free fatty acids (FFAs) [9]. Adipocytes not only function as energy storage cells by providing FFAs for fueling cancer cells, but also serve as endocrine cells by secreting cytokines and chemokines to modulate tumor growth, metastasis, and cachexia [12].

Cancer-associated adipocytes (CAAs) are adjacent adipocytes located at the invasive front of human breast tumors that can enhance cancer progression [13,14]. Compared with mature adipocytes, CAAs exhibit a fibroblast/myofibroblast-like phenotype, including smaller cell sizes, irregular shapes, dispersed small lipid droplets, and inflammatory cytokine overexpression. In addition, compared with mature adipocytes, CAAs have decreased expression of adipocyte differentiation biomarkers, such as CCAAT enhancer binding protein alpha, peroxisome proliferator-activated receptor gamma, and fatty acid binding protein 4, with increased expression of specific biomarkers, including uncoupling protein 1, alpha-smooth muscle actin, and E-cadherin [15–17]. Besides, CAA-derived cytokines, including IL-6, interleukin-8 (IL-8), IL-1β, C–C motif chemokine ligand 5 (CCL5), CCL2, vascular endothelial growth factor (VEGF), granulocyte colony-stimulating factor (G-CSF), insulin-like growth factor-1 (IGF-1), and insulin-like growth factor binding protein (IGFBP), are crucial participants in breast cancer progression. In brief, CAAs gain a more vicious phenotype to enhance breast cancer growth and metastasis than ordinary mature adipocytes (Fig. 1).

CAAs adjacent to human breast tumors exhibit a fibroblast/myofibroblast-like phenotype, including smaller cell sizes, irregular shapes, dispersed small lipid droplets, and different biomarkers compared with normal breast adipocytes. In CAAs, mature adipocyte biomarkers (CEBP-α, PPAR-γ, APM-1, FABP4, and GLUT4) are decreased, and undifferentiation biomarkers (UCP-1, α-SMA, E-cadherin, fibronectin, WNT10b, and GATA2) are increased. Abbreviations: CAA, cancer-associated adipocyte; CEBP-α, CCAAT enhancer binding protein alpha; PPAR-γ, peroxisome proliferator-activated receptor gamma; AMP-1, adenosine monophosphate 1; FABP4, fatty acid binding protein 4; GLUT4, glucose transporter 4; UCP-1, uncoupling protein 1; α-SMA, alpha-smooth muscle actin; WNT,

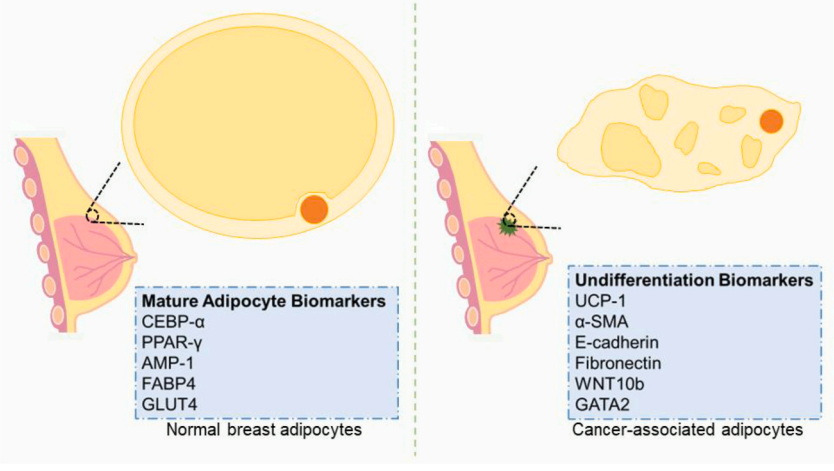

Fig. 1. Comparison between normal breast adipocytes and cancer-associated adipocytes.

wingless-related integration site; GATA, GATA binding protein.

CAAs are involved in breast tumor initiation, progression, invasion, and metastasis. Intriguingly, CAAs are intensively related to the immune regulation of breast cancer. For example, macrophages play an essential role in the crosstalk between adipocytes and cancer cells. Dead or dying adipocytes and surrounding macrophages form crown-like structures (CLSs) in breast tissue regardless of the presence of breast cancer, which represent a histologic hallmark of the pro-inflammatory process [18,19]. The formation of CLSs can be regarded as a sign of the beginning of crosstalk between CAAs and breast cancer cells. Moreover, small CLSs that are found at the invasive border of breast cancer are presumed to be generated from CAAs with characteristics, such as reduced size due to lipolysis, modification of lipid droplets, and remodeled ECM [18]. There are also other immune cells taking part in CAA-associated tumor promotion in TME, such as neutrophils, T cells, B cells, and monocytes [10].

Therefore, CAAs are capable to regulate tumor cell behaviors and the immune status of breast cancer. Here, we aim to provide a comprehensive description of CAA-derived cytokines, including their impact on cancer cell behaviors, immune regulation, breast cancer diagnosis, and therapy.

2. CAA-derived cytokines in regulating breast cancer progression

2.1. IL-6

IL-6 is a pleiotropic cytokine involved in pathophysiological processes, such as immune responses, inflammation, hematopoiesis, tissue repair, and bone metabolism [20]. The classical IL-6 family includes IL-6, IL-11, IL-27, IL-35, IL-39, oncostatin M (OSM), leukemia inhibitory factor (LIF), ciliary neurotrophic factor, cardiotrophin-1, and cardiotrophin-like cytokine factor 1 [21]. Adipose stromal cells with multipotent potential could secrete IL-6 to stimulate the invasion and migration of breast tumor cells by promoting the Cofilin-1-dependent pathway [22]. Pre-adipocytes significantly upregulated IL-6 secretion and displayed more elongated fibroblast morphology while co-culturing with breast cancer cells [23]. The overproduction of adipocyte-derived IL-6 led to the proliferation and migration of breast cancer cells.

As another multifunctional member of the IL-6 family, LIF participates in substantial physiological and pathological processes, and is overexpressed in various types of solid tumors, including breast cancer [24]. CAA-derived LIF promoted triple-negative breast cancer (TNBC) cell progression by activating the STAT3 signaling [14]. Importantly, LIF and CXCLs could regulate mutually between breast cancer cells and CAAs, which formed a positive feedback loop to accelerate the progression of breast cancer.

As for a cancer metastasis promoter, OSM positively adjusts metastatic transition, such as cell-substrate detachment, ECM degradation, and EMT [25]. Moreover, Lapeire et al. demonstrated that cancer-associated adipose tissue boosted breast cancer progression by increased paracrine OSM and activated STAT3 signaling [26]. There was a significant upregulation of S100A7 stimulated by OSM to induce cellular scattering and migration. Doherty et al. also discovered that OSM overexpression could repress endogenous interferon beta (IFN-β) mRNA and induce the aggressiveness of TNBC cells in the TME [27]. OSM and the associated decrease of IFN-β accelerated breast tumor growth and migration through activation of JAK/STAT and MAPK signaling pathways.

2.2. IL-8

IL-8, known as CXCL8, is a pro-inflammatory CXC chemokine [28]. It is widely recognized that IL-8 plays a role in angiogenesis, migration, and invasion in numerous solid tumors. A prospective observational study investigated 92 immuno-oncology proteins in serum from 136 metastatic breast cancer patients, showing that high serum levels of IL-8 were considerably related to worse overall survival (OS) and progression-free survival [29]. CAAs increased the secretion of IL-8 to trigger the EMT effect in breast luminal cells in a paracrine manner [30]. Moreover, IL-8 upregulation in CAAs was accompanied by activating STAT3 signaling. This study also attested that IL-8 knockdown could suppress proliferation capability and the cancer-promoting effects of CAAs. Vazquez et al. concluded that breast adipocytes modified the TME toward a pro-inflammatory condition by enhancing IL-8 secretion [31]. Neutralization of IL-8 altered cytokine secretion of breast adipocytes with reduced CCL5 and VEGF, which in turn decreased breast cancer cell dissemination.

2.3. IL-1β

IL-1 is a pro-inflammatory cytokine secreted by adipose tissue in breast cancer development [32]. It contains two main isoforms, IL-1α and IL-1β, which have complementary or contrasting functions in different types of cancers [33]. IL-1 is considered an upstream alarm signal since the minor production of IL-1 can induce potent secondary responses of other mediators in cancer progression [34]. In obese breast tumors, the upregulation of adipocyte-derived IL-1β acted collectively with hypoxia to induce ANGPTL4 expression of primary adipocytes through activation of NF-κB and JNK signaling [35]. Furthermore, ANGPTL4 from adipocytes was beneficial to breast cancer angiogenesis and progression under obese conditions, and was a potential therapeutic target for obese breast cancer patients.

2.4. CCL5

CCL5, which is alternatively known as RANTES, mediates the migration and chemotaxis of inflammatory cells, including memory T lymphocytes, monocytes, and eosinophils [36]. In addition, CCL5 is positively correlated with axillary lymph node metastasis and poor

prognosis in breast cancer. D'Esposito et al. discovered that CAA-derived CCL5 contributed to enhanced motility and invasiveness of TNBC cells [37]. Inhibition of CCL5 in the adipose microenvironment reduced TNBC cell aggressiveness. Coincidentally, Song et al. reported that adipocytes increased the secretion of CCL5 to promote the EMT effect of co-cultured TNBC cells and further accelerated lung and liver metastasis in vivo of mice [38]. Consequently, they proposed that CCL5 inhibitor emodin could remodel the adipose microenvironment, suggesting a novel therapeutic target for breast cancer.

2.5. CCL2

CCL2, which is also referred to as monocyte chemoattractant protein 1, is an effective inducible chemokine that recruits immune cells, in particular monocytes, to infiltrate into the inflammatory tissue region. CAAs increased CCL2 secretion to facilitate tumor progression and exacerbate immunosuppressive TME when co-cultured with TNBC cells [39]. Targeting CAA-derived CCL2 could decrease M2 macrophage and myeloid-derived suppressor cell (MDSC) population and increase T cell infiltration, enhancing the efficacy of immunotherapy in TNBC. Adipocytes promoted cancer cell migration in the presence of breast cancer cells via upregulating the secretion of CCL2 and IL-6 [17]. Using antibodies against CCL2 or IL-6 showed the abolishment of the migration-enhancing effect of the CAA-conditioned medium. Arendt et al. demonstrated that the enhanced CCL2 and IL-1β produced by breast adipose tissue, induced macrophage recruitment and CLS formation in obese breast cancer patients, which further induced angiogenesis [40]. Furthermore, adipocyte-derived CCL2 cooperated with IL-1β to promote the induction of CXCL12 in macrophages, and the activation of the CCL2/IL-1β/CXCL12 pathway contributed to angiogenesis in obese breast cancer.

2.6. VEGF

VEGF is an essential angiogenic factor that stimulates downstream signaling cascades via binding to VEGF receptors with distinct affinity and specificity [41]. VEGF signaling can also activate MMP-2, MMP-9, and urokinase plasminogen activators, which degrades the ECM and basal membrane system. Generally speaking, the activated VEGF pathway supports the survival, proliferation, and migration of endothelial cells, promoting immune tolerance, and inducing vascularization of breast cancer.

Therefore, Bougaret et al. used a co-cultured model of mature adipocytes and breast cancer cells to mimic the angiogenic process of the adipocyte microenvironment surrounding mammary tumors [42]. Supernatants from co-cultures of mature adipocytes and MCF-7 cells enhanced the proliferation, migration, and vascularization of human umbilical vein endothelial cells regardless of female body mass index. Neutralizing antibodies of VEGF and leptin could counteract the formation of new vessels and the dissemination of breast cancer cells. Additionally, Paino et al. indicated that human adipose stem cells, co-injected with breast cancer cells, could release more VEGF in the TME to promote vessel growth and tumor metastasis [43].

2.7. G-CSF

G-CSF is an essential member of the hematopoietic growth factor family regulating granulopoiesis. G-CSF stimulates neutrophil proliferation, differentiation, and activation as well as decreases neutrophil maturation time [44]. G-CSF is reported to be tumorigenic in plentiful preclinical studies. CAA-derived G-CSF could enhance breast cancer migration and invasion through activating STAT3 signaling and could cooperate with other CAA-derived factors IL-6 and granulocyte-macrophage colony-stimulating factor (GM-CSF) to form an amplification effect on breast cancer progression [45]. GM-CSF, known as CSF2, was highly expressed in breast cancer cells and adipocytes, and increased CAA-derived CXCL3 expression by activating STAT3 signaling [46]. CAA-derived CXCL3 promoted the migration and invasion of breast cancer cells in vitro and induced lung metastasis in mice. Moreover, G-CSF was identified as one of the most highly upregulated genes in CAAs and was upregulated in breast cancer-associated adipose tissue. Thus, targeting the CAA-derived G-CSF axis might be effective for interventing malignant breast cancer. Higara et al. found that G-CSF suppressed breast cancer cell homing to the bone by downregulating CXCL12 expression in bone marrow stromal cells, however, G-CSF could induce bone metastasis partly by MDSC-mediated mechanisms [47]. Despite the opposing effects of G-CSF on the initiation and progression of breast cancer bone metastasis, the complicated G-CSF role deserved further investigation as a therapeutic strategy for bone metastasis.

2.8. IGF-1 and IGFBP

IGF-1 with a similar molecular structure and signaling pathways to insulin is involved in the progression and development of various cancers, such as gastrointestinal, gynecological, lung, prostate, and breast cancers [48]. IGFBP is a group of proteins with high affinity to IGF-1, thus competing with IGF-1R for binding to IGF-1 and degrading IGF-1 bioavailability.

IGF-1 attenuated the response of the MCF-7 cell line to doxorubicin (DOX) and paclitaxel by inducing breast cell proliferation and inhibiting cell apoptosis [49]. High plasma levels of IGF-1 and IGFBP represented a risk indicator of the development and recurrence of breast cancer. Moreover, crosstalk between IGF-1 and leptin was reported to induce migration and invasion of breast cancer cells [50]. Wang et al. discovered that the co-culture of breast cancer cells with adipocytes enhanced the production of IGFBP by adipocytes, which then promoted breast cancer both in vitro and in vivo [51]. Moreover, CAA-derived IGFBP-2 promoted the invasion ability of MCF-7 cells in vitro more prominently than other soluble factors. Since IGFBP-2 from adipocytes could upregulate MMP-2 in MCF-7 cells to enhance invasion and metastasis of breast cancer, CAA-derived IGFBP-2 might become a new target to reduce the extent of breast cancer metastasis (Fig. 2).

Cytokines (IL-6, IL-8, IL-1β, CCL5, CCL2, VEGF, G-CSF, and IGF-1) from CAAs can affect cancer progression by promoting malignant

behaviors (proliferation, angiogenesis, EMT, migration, and metastasis) of breast cancer cells. Abbreviations: CAA, cancer-associated adipocyte; IL-1, interleukin-1; CCL5, C–C motif chemokine ligand 5; VEGF, vascular endothelial growth factor; G-CSF, granulocyte colony-stimulating factor; IGF-1, insulin-like growth factor-1; STAT3, signal transducer and activator of transcription 3; MAPK, mitogen-activated protein kinase; NF-κB, nuclear factor-kappa B; PI3K/AKT, phosphatidylinositol 3 kinase/protein kinase B; ERK, extracellular regulated protein kinase 1/2; EMT, epithelial-to-mesenchymal transition.

2.9. Others

Except for the above-mentioned CAA-derived factors, there are other members of the CAA secretome that are involved in breast cancer progression. CAAs expressed PLOD2 to mediate collagen reorganization in the TME, which led to tumor invasion and metastasis [52]. He et al. revealed that adipocyte-derived IL-6 and leptin facilitated PLOD2 expression by activation of JAK/STAT3 and PI3K/AKT signaling pathways. Nevertheless, Wei et al. found that neutralization of IL-6 did not abrogate PLOD2 in CAAs and that breast cancer cells secreted plasminogen activator inhibitor type 1 to induce PLOD2 activation through activating the PI3K/AKT pathway [53]. Presumedly, targeting PLOD2 might be a credible strategy to prevent the malignant progression of breast cancer. It was proved that breast tumor cells modified CAAs by secreting adrenomedullin, which led to metabolic changes and delipidation in adipocytes [54]. Interestingly, Reilly et al. reported that catecholamines released in adipose tissue could suppress fatty acid reesterification to increase oxidation in white adipocytes through the phosphorylation of STAT3, which provided fatty acids (FAs) for surrounding tissues [55].

3. CAAs in immune regulation of breast cancer

Tumor immune microenvironment (TIME) contains many immune cell types that can interact with each other, such as innate immune cells, adaptive immune cells, and MDSCs [56]. Macrophages are one of the most important and frequently studied immune cells in breast cancer TIME and are clearly involved in metastasis, chemoresistance, and immunosuppression in breast cancer. Moreover, macrophages are categorized into two interconvertible states, inflammatory M1 macrophages and anti-inflammatory M2 macrophages [57,58]. M1 macrophages recognize and destroy cancer cells through phagocytosis and cytotoxicity, whereas M2 macrophages boost tissue repair and tumor growth [59].

In obese circumstances, the massive growth of adipose tissue contributes to hypoxia, adipocyte stress, and increased release of inflammatory cytokines, thereby exhibiting a chronic tissue injury microenvironment [60]. These incremental adipokines reciprocally result in inflammation-associated obesity, which might boost the growth and metastasis of breast cancer [61]. Especially in obese

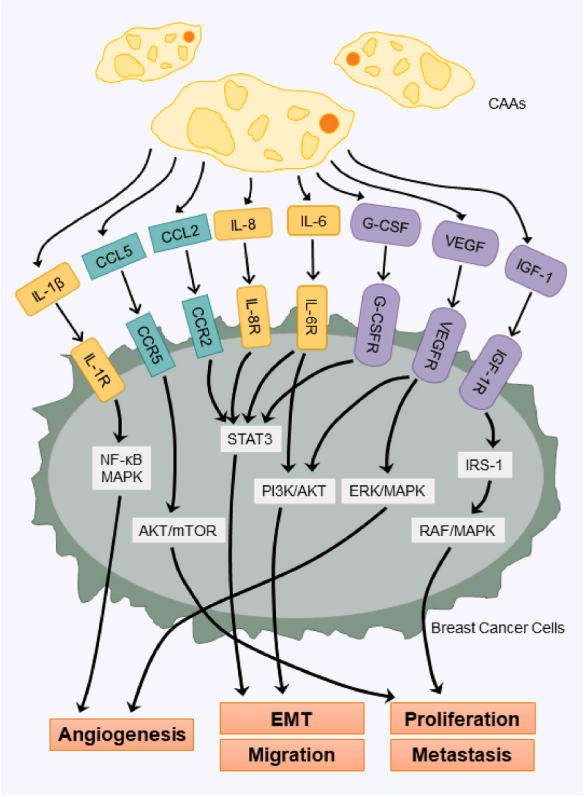

Fig. 2. CAA-derived cytokines in regulating breast cancer progression.

breast cancer patients, dysfunctional adipose tissue enhances the malignant behaviors of breast tumor by increasing the secretion of pro-inflammatory molecules from adipocytes, precipitating immune cell recruitment and macrophage polarization, as well as reinforcing tumor cell invasion, migration, and EMT [11,62,63].

Cytokines and chemokines, as indispensable components of TIME, are essential mediators and regulators of immune cell migration, infiltration, and bioactivity. IL-6, TNF-α, and leptin from human breast adipocytes could increase macrophage-derived VEGF-A in TME to stimulate endothelial tube formation, thus promoting tumor angiogenesis and breast cancer metastasis [64]. CAA-derived IL-6 could stimulate M2 polarization by activating the STAT3 pathway, leading to the proliferation, invasion, and metastasis of TNBC cells [65]. High levels of IL-8, generated from breast adipocytes, induced a tumor-promoting activation of neutrophils via increasing lymphocyte function-associated antigen 1 (LFA-1) expression in neutrophils, which further increased the migration capacity of breast cancer cells [31]. In the zebrafish model of metastasis, blocking the activity of IL-8 and LFA-1 inhibited neutrophil recruitment, and significantly suppressed breast cancer cell dissemination. Moreover, higher IL-8 expression from CAAs promoted the EMT process in TNBC by activating the PI3K/AKT pathway, and contributed to immunosuppressive TME by increasing CD274 expression and decreasing T and B cell infiltration [66]. Vazquez et al. reported that neutrophils responded to microenvironmental cues and played a significant role in the early stages of BC metastasis [67]. Obesity-associated NLRC4 inflammasome induced IL-1β activation in tumor-associated macrophages (TAMs), which then elevated VEGF-A expression of primary adipocytes and promoted breast cancer angiogenesis and growth [68]. Neutrophils could secrete extracellular structures called neutrophil extracellular traps (NETs) to trap and kill bacteria [69]. G-CSF induced NET formation and promoted breast cancer growth in tumor-bearing mice [70].

In terms of chemokines, CCL5/CCR5 could affect the polarization of M2 macrophages through the activation of the MEK/STAT3 and ERK1/2 signaling pathways in luminal B breast cancer [36,71]. In addition, the knockdown of CCR5 expression in macrophages blocked the polarization process, thus restraining the progression of breast cancer and metastasis. CAAs potentiated angiogenesis indirectly by secreting CCL2 to recruit and reprogram macrophages into breast tumors [72]. CCL2 from adipocytes promoted the polarization of TAMs to the M2 phenotype, which inhibited the antitumor immune response and mediated the occurrence and development of breast cancer. Coincidentally, Santander et al. demonstrated that the elevated CCL2 from 3T3-L1 pre-adipocytes mediated macrophage recruitment and promoted TAM infiltration in tumors when co-cultured with mammary tumor cells [73]. They also found that the amount of macrophages/CLS and inflammatory factors was higher in TME from obese rather than lean tumor-bearing mice, and that mammary tumors were larger in obese mice.

There are other multiple adipokines released from CAAs, participating in the immunoregulation of TME. For instance, Zhang et al. revealed that in obesity-associated breast cancer, adipocyte-derived leptin combined with leptin receptor in $CD8^+$ T cells to induce FA oxidation metabolism in T cells, and consequently led to T cell incapacity to impair antitumor immune response through STAT3 signaling upregulation [74]. Adipocite-derived FFAs could activate toll-like receptor 4 on the macrophage plasma membrane, leading to raised NF-κB dependent secretion of TNF-α [60]. TNF-α and other adipokines further stimulated lipolysis and release of FFAs, which maintained the inflammatory status of adipose tissue (Fig. 3).

Adipocytes can regulate immune cells in the TME of breast cancer. Adipocytes secrete soluble factors to suppress the antitumor function of NK cells and $CD8^+$ T cells. Moreover, CCL2/IL-1β/CXCL12 from CAAs induces recruitment and M2 polarization of macrophages. In addition, dead or dying adipocytes and surrounding macrophages form CLSs, which promote breast cancer initiation and angiogenesis. Abbreviations: IL-8, interleukin-8; FFA, free fatty acids; CLS, crown-like structure; CXCL12, C-X-C motif chemokine

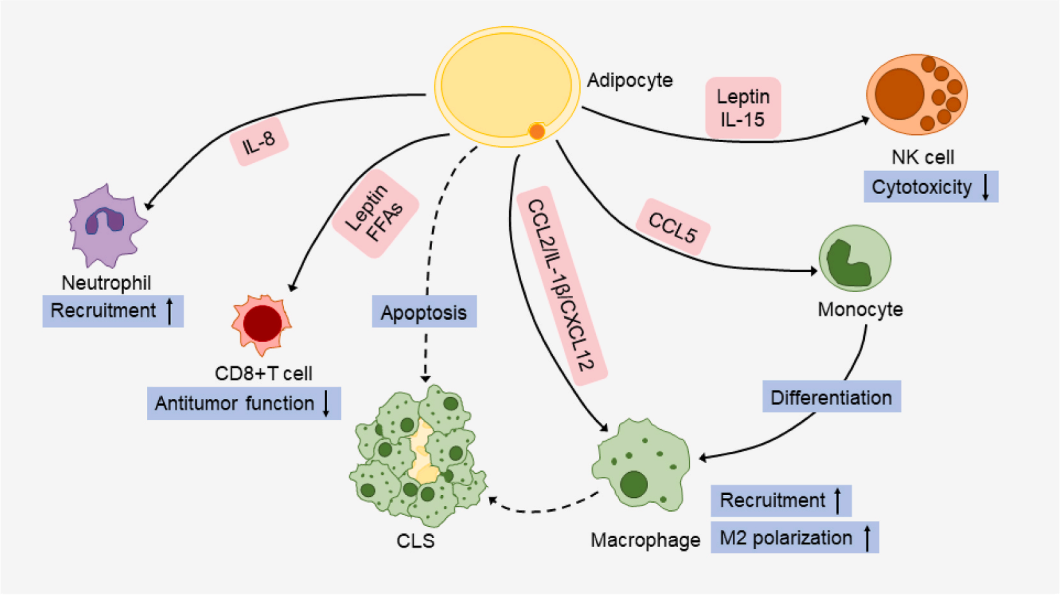

Fig. 3. The roles and mechanisms of adipocytes in immune regulation of breast cancer.

ligand 12; CAAs, cancer-associated adipocytes; CCL5, C–C motif chemokine ligand 5; NK cell, natural killer cell.

4. CAAs in breast cancer therapy

The conventional treatment strategies for patients with breast cancer consist of surgery, chemotherapy, radiotherapy, hormonal therapy, and targeted therapy. Most of these strategies target cancer cells, but current therapy development gradually focuses on targeting components of the TME. Based on the interfering crosstalk between adipose tissue and breast cancer, the mechanisms of adipose-associated treatment can be divided into the following aspects: (i) inhibiting adipogenesis, (ii) suppressing the adipose secretome, and (iii) blocking signals from breast cancer cells which regulate adipose tissue behavior. Since the expression profile of various cytokines produced by CAA is altered, which can significantly promote breast tumor growth and metastasis, blocking CAA-derived cytokines is expected to be a meaningful cancer treatment. There have been several experimental studies on breast cancer treatment targeting CAA-derived soluble factors. In obese mice, IL-6 inhibition reduced CXCL1 and thus decreased immunosuppressive cell recruitment of $CD4^+$ T cells and regulatory T cells, which might strengthen the immunotherapy effect of breast cancer [75]. Bonapace et al. confirmed that CCL2 neutralization in mice inhibited breast cancer metastasis by retaining monocytes in the bone marrow [76]. However, the immediate cessation of anti-CCL2 treatment triggered a rebound effect in CCL2 and IL-6 expression, resulting in enhanced local angiogenesis, increased monocyte infiltration, and accelerated metastasis. Therefore, a restricted and transient CCL2 blockade might be effective in modifying immunosuppressive TME with reduced systemic toxicity.

Mastectomy is considered a very reliable therapy for breast cancer, and there is an increasing emphasis on post-operative breast reconstruction. Lipofilling, also named autologous fat graft (AFG), is widely applied to breast reconstructive surgery after mastectomy or breast-conserving surgery [77]. The fat tissue from liposuction is transplanted into the breast to obtain a better breast morphology. The application of adipose-derived stem cells (ADSCs) has significantly expanded in reconstructive and plastic surgery, however, liposuction shrinks the amount of ADSCs due to mechanical damage [78,79]. Therefore, cell-assisted lipotransfer can improve this shortage with additional and concentrated ADSCs. Considering the tumor-promoting effects of CAAs, the oncologic safety of AFG after mastectomy for breast cancer is certainly more of a concern than cosmetic satisfaction. Some studies showed that ADSCs could enhance the oncogenic capability of active breast cancer cells by secreting cytokines [77,80,81]. However, Krastev et al. confirmed that locoregional recurrence (LRR) did not increase among more than 4000 breast cancer patients who experienced AFG across 59 studies [80]. A limitation of this meta-analysis was the short follow-up period of about three years after AFG [81]. Since this study aimed to verify the association between AFG and the risk of breast tumor recurrence, a longer follow-up period of at least five years would be more reliable. Sun et al. also conducted a systematic assessment including 11 studies and 5886 patients, and showed that AFG was not obviously related to LRR and disease-free survival [82]. According to current evidence, AFG is oncologically safe for breast reconstruction after mastectomy, and prospective randomized controlled clinical trials with appropriate follow-up are required.

5. Limitations and perspectives

Voluminous studies have attempted to illuminate the exquisite mechanisms of CAAs in breast cancer, and multiple cytokines from CAAs have been validated to participate in the reconstruction of TME. Here, we emphasize CAA-derived cytokines (IL-6, IL-8, IL-1β, CCL5, CCL2, VEGF, G-CSF, IGF-1, and others), but some other specific cytokines are not reported due to different cytokine types and limited detection techniques. However, some aspects of the crosstalk between CAAs and breast cancer cells still deserve further exploration, including molecular mechanisms, immune regulation, and therapeutic strategy. The Wnt/β-catenin and Notch signaling pathways are currently the main interpretations for CAA formation induced by cancer cells [83]. Inflammatory factors secreted by cancer cells also lead to CAA transformation through suppressing PPAR-γ expression in adipocytes by activating the NF-κB pathway [16]. Moreover, exosomes from breast cancer cells can induce CAA formation by transporting the cargo miRNAs and proteins [84]. For instance, Rybinska et al. identified that serum amyloid A1 (SAA1), a well-recognized acute-phase protein, could be released from TNBC cells and could drive the reprogramming of peripheral adipocytes [85]. TNBC-expressed SAA1 bound to P2X7R and CD36 receptors on adipocytes and activated downstream NF-κβ and JNK pathways, reverting adipocytes to a CAA phenotype. Co-cultured with Met-1 and EO771 breast cancer cells, normal adipocytes were transformed into CAAs through TGF-β/Smad pathway, and FAM3C expression in CAAs was upregulated by TGF-β [86]. CAA-derived FAM3C supported tumor initiation by reducing cell death and fibrosis in early breast cancer stages, and promoted metastasis by enhancing EMT and migration of cancer cells in later tumor stages, possibly through ERK pathway activation.

Firstly, there are some characteristic cytokines and adipokines secreted from adipocytes that could regulate the activity of tumors and the immune effect of TME to promote or suppress breast cancer evolution. With the rapid development of new sequencing technologies, including single-cell omics, metabolomics, proteomics, and spatial transcriptomics, the mysterious potential adipocyte secretion profiles and key molecules as promising potential diagnostic and therapeutic targets are able to be revealed. Currently, the isolation of intact and individual adipocytes remains challenging due to their vulnerable characteristics, so similar sequencing means have not been fully applied in human adipose tissue. Nevertheless, these techniques will certainly be of great use in exploring the extensive range of adipocyte heterogeneity and molecular functions. These will contribute to identifying different adipocyte types, such as pre-adipocytes, normal breast adipocytes, CAAs, and adipose stromal cells. Emont et al. performed single-nucleus RNA sequencing, which could capture mature adipocytes, to identify cell types in adipose tissue, and found that there were 7 adipocyte subpopulations in human WAT [87]. Similarly, Liu et al. addressed that their single-cell atlas revealed different adipocyte subpopulations in mouse and human WAT [88]. However, single-nucleus RNA sequencing was not directly applied to CAAs, which indicated that the specific characterization and potential interrelationship of CAAs at single-cell resolution remained lacking in breast

cancer. Furthermore, the origin of cytokines and chemokines in TME deserves to be noticed. Multiple cell types and polyfunctional soluble active factors congregate in the complex TME of breast cancer. For instance, IL-6 can be released by tumor cells, primary adipocytes, or immune cells, and the IL-6R is also expressed in these cell types correspondingly [20,22,89]. Owing to the intricate network of cytokines, the specific CAA-secreted cytokines remain to be determined under certain circumstances. Although cellular experiments verify the correlation between certain CAA-derived factors and breast cancer cells, the actual interactive objects in TME are difficult to detect in animals or patients. The mechanism that remodels TME by interacting with immune cells deserves exploring. Immune cell types regulated by CAA-derived cytokines lack in-depth investigation, as most studies concentrate on macrophages in TME rather than MDSCs, neutrophils, or B lymphocytes.

Except for traditional therapeutic strategies including surgery, chemotherapy, radiotherapy, hormonal therapy, and immunotherapy, there are some novel research directions for breast cancer treatment. As requisite extracellular vesicles (EVs), exosomes are formed and released by budding from the plasma membrane [90]. Exosomes act as a reservoir that contains genetic and functional molecules, including nucleic acids (DNA, mRNA, ncRNAs), enzymes, and proteins. During tumor metastasis, CAAs interact with breast tumor cells by secreting soluble factors and EVs in TME. Additionally, by utilizing the carrier function of exosomes, therapeutic strategies can be developed by modifying exosomes with high levels of tumor antigens or certain chemokines [91]. These antigen-anchored or chemokine-carried exosomes can efficiently recruit antitumor immune cells to the tumor location and prompt tumor-specific cytotoxicity and tumor cell death. Moreover, unraveling the complexity of the adipocyte secretome could contribute to the development of targeted therapies to overcome drug resistance mechanisms in breast cancer. Bochet et al. first proposed that tumor-surrounding adipocytes could foster radioresistance in breast cancer cells by overexpressing IL-6 [92]. Adipocyte-secreted IL-6 activated STAT3 signaling to increase prosurvival genes bcl-X and survivin expression and promoted Chk1 phosphorylation to prevent tumor cell death from infrared radiation exposure, which enhanced the radioresistance of breast tumor cells. Wellberg et al. found that adipocytes upregulated fibroblast growth factor 1 (FGF1) expression in obese tissue, which promoted FGFR-1 expression in breast cancer cells after estrogen deprivation [93]. FGFR1 phosphorylation represented a worse therapeutic effect and shorter survival for tamoxifen-treated patients. Adipose-derived mesenchymal stem cells enhanced breast cancer resistance protein expression by IL-8 overproduction, leading to DOX resistance in TNBC cells [94]. Co-cultured with breast tumor cells, adipocytes could approve DOX efflux by increasing the number of EVs secreted by tumor cells and the amount of DOX in vesicles [95]. Vazquez et al. reported that in the zebrafish model, an interconnection of IL-8, CCL2, and CCL5 might be implicated in anti-VEGF resistance of ER-negative breast cancer treatment [31]. They found that anti-VEGF could upregulate IL-8 expression of breast adipocytes, and the neutralization of IL-8

Table 1
CAA-derived cytokines in different breast cancer subtypes.

Cytokine type	Breast cancer subtype	Mechanism	Progression	Reference
FAM3C	Luminal B TNBC	Activating ERK pathway	Promoting cancer cell proliferation and EMT	[86]
IL-6	TNBC Non-TNBC	Activating JAK/STAT3 and PI3K/AKT pathways, upregulating PLOD2	Promoting cancer cell migration and invasion	[52]
	TNBC	Inducing M2 polarization of macrophages via activating STAT3 pathway	Supporting cancer cell proliferation, invasion, metastasis and EMT	[65]
LIF	TNBC	Activating STAT3 pathway	Promoting cancer cell migration and invasion	[14]
IL-8	TNBC	Activating PI3K/AKT pathway, upregulating CD274	Promoting EMT, inhibiting immune response	[66]
	HER2 Luminal A	Activating STAT3 pathway	Promoting EMT, angiogenesis	[30]
	Luminal A TNBC	Upregulating cell-adhesion molecules in cancer cells and neutrophils	Promoting cancer cell dissemination, angiogenesis	[31]
OSM	Luminal A	Upregulating S100A7, activating STAT3 pathway	Promoting inflammation, invasiveness, angiogenesis	[26]
	TNBC	Activating STAT3/SMAD3 pathway, upregulating SNAIL	Promoting tumor initiation, growth	[27]
Iβ	TNBC	Activating NF-κB and JNK pathways, upregulating ANGPTL4	Promoting tumor angiogenesis, growth	[35]
CCL5	Luminal A Luminal B HER2 TNBC	Activating CCL5/CCR5 pathway in Tregs	Promoting axillary lymph node metastasis	[36]
	TNBC	Activating AKT pathway	Promoting EMT	[38]
CCL2	TNBC	Not mentioned	Enhancing immunosuppressive TME	[39]
	Not mentioned	Activating CCL2/IL-1β/CXCL12 pathway	Promoting inflammatory macrophage recruitment, angiogenesis	[40]
VEGF	Luminal A	Not mentioned	Promoting tumor angiogenesis	[43]
G-CSF	TNBC	Activating STAT3 pathway	Promoting cancer cell migration and invasion	[45]
	TNBC	Downregulating CXCL12 in BMSCs	Promoting bone metastases	[47]
GM-CSF	TNBC	Activating STAT3/CXCL3/FAK pathway	Promoting EMT	[46]
IGF-1	Luminal A TNBC	Transactivating EGFR, activating AKT and ERK pathways	Promoting cancer cell proliferation, migration, invasion	[50]
IGFBP-2	Luminal A	Not mentioned	Promoting cancer cell migration and invasion	[51]

tremendously decreased CCL5 secretion in MCF-7/adipocyte co-cultures, which correspondingly suppressed breast cancer cell dissemination. Thus, IL-8 from breast adipocytes was responsible for anti-angiogenesis therapy resistance. It is necessary to distinguish drug resistance in clinical practice from that in the experiment. Whether CAA-targeted treatment could reverse drug resistance in clinical practice remains in doubt.

Currently, the studies on CAAs in breast cancer mainly focus on the following breast cancer subtypes, estrogen receptor (ER) -positive, ER-negative, TNBC, non-TNBC, Luminal A, and other unspecific subtypes (Table 1). In particular, TNBC takes up nearly 15 % of all invasive breast cancer, and possesses the highest rate of tumor metastasis and the shortest OS in all breast cancer subtypes. CAAs can enhance the capacity of TNBC cells to migrate and invade. However, many CAA-related studies do not emphasize specific subtypes of breast cancer clinical samples, such as molecular subtypes, pathological classification, and TNM staging, which is worthy of consideration in highly heterogeneous breast cancer. The existing original studies mainly focus on the specific breast cancer subtypes that researchers are concerning about, but lacking the comparison between breast cancer subtypes. Additionally, different subtypes of breast cancer may exhibit distinct responses to the secretome of CAAs. CAA enhances the migratory and invasive properties of both ER-positive and negative breast cancers, but which breast cancer subtype CAA promotes more significantly remains controversial. Besides, the specific CAA-secreted factor that plays a major role in different tumor staging needs to be determined. Comprehensive characterization of the CAA secretome using high-throughput screening techniques, such as proteome analysis, serves to identify specifically expressed or differentially regulated cytokines in different breast cancer subtypes. With these data, we can construct an exhaustive CAA secretome atlas, providing a basis for understanding the role of CAAs in breast cancer heterogeneity. In addition, accurate biomarkers for CAA identification and secretome profile are critical for improving the early diagnosis or prognostic assessment of breast cancer. For example, developing diagnostic tools and therapeutic strategies based on the CAAs secretome, such as monoclonal antibodies or small molecule inhibitors targeting specific cytokines, facilitates the translation from laboratory discoveries to clinical applications. Adjustment of CAA-derived cytokines through gene editing techniques, such as CRISPR/Cas9, allows the development of new therapeutic strategies for breast cancer. Further, existing immunotherapeutic strategies, such as immune checkpoint inhibitors, potentially exert the effects by altering the interactions between CAAs and immune cells. The combination of CAA-targeted therapies and immunotherapy may become a prevalent treatment for breast cancer.

Fat grafting is standardized and widely popularized in breast reconstruction. Conducting large-scale clinical trials with long-term follow-up is necessary to ensure the oncologic safety of breast cancer patients after mastectomy. AFG needs sensitive and strict monitoring indexes to prevent breast cancer patients from the potential recurrence after surgery. Furthermore, high-quality clinical studies ought to provide specific criteria, such as breast cancer subtypes and TNM staging, for the application of AFG, as well as definite surgical kinds of AFG. At present, there is no unified identification standard for CAAs. In addition to identifying CAA-associated gene and protein biomarkers, further research is needed to characterize CAAs for breast cancer diagnosis, treatment response prediction, and prognosis evaluation. Residual adipose tissue around breast tumors may lead to recurrence after mastectomy, indicating the importance of precise boundaries for adipose tissue removal. Accurate biomarkers for CAA identification are critical for plastic surgeons to ensure whether CAA-containing adipose tissue contributes to breast cancer recurrence and whether residual CAAs may interfere with recovery after fat grafting.

6. Conclusion

The crosstalk between breast tumor cells and adipocytes is dynamic, volatile, and elaborate. Adipocytes and breast cancer cells are capable to respond to endocrine and paracrine signals within TME. Cancer cells can revert neighboring adipocytes to a CAA phenotype. Reciprocally, CAAs stimulate the invasiveness and metastatic potential of tumor cells by promoting the immunosuppressive TME. CAAs are no longer considered passive bystanders, but rather the dominant character contributing to breast cancer progression, metastasis, and chemo-resistance via adipocyte secretome. CAAs can be defined as follows: (i) cancer cells significantly impact peripheral adipocytes; (ii) peripheral adipocytes exhibit a modified fibroblast/myofibroblast-like phenotype and unique biological characteristics adequate to be named CAAs; (iii) soluble cytokines (IL-6, IL-8, IL-1β, CCL5, CCL2, VEGF, G-CSF, IGF-1, etc.) and adipokines (leptin, resistin, adiponectin, visfatin, etc.) from adipocytes are characterized differently during cancer development and have been demonstrated in vitro, in vivo, and in human breast cancer samples.; and (iv) CAAs are vicious components in TME and can alter breast cancer cells into a more aggressive phenotype.

Overall, CAA-derived cytokines affect breast cancer cells, immune cells, and vascular endothelial cells via paracrine function, thereby influencing cancer cell activity, angiogenesis, and immune regulation of TME, and ultimately reshaping breast cancer behavior. A deeper understanding of CAA's roles and mechanisms will provide novel therapeutic strategies for combating breast cancer.

Ethics approval

Not applicable. Review and/or approval by an ethics committee was not needed for this study because this study involved a comprehensive analysis of existing literature and did not involve any primary data collection or experiments that would require ethical considerations.

Consent for publication

All the authors agreed to be published.

Availability of data and materials

Not applicable. No data was used for the research described in the article.

Funding

This work was supported by Nature Science Foundation of Hubei Province (2022CFB177).

CRediT authorship contribution statement

Zihui Yang: Writing – original draft, Conceptualization. **Hong Zeng:** Writing – original draft. **Jia Li:** Writing – original draft. **Ning Zeng:** Investigation. **Qi Zhang:** Investigation, Conceptualization. **Kai Hou:** Investigation. **Jie Li:** Writing – review & editing, Supervision. **Jing Yu:** Writing – review & editing, Supervision. **Yiping Wu:** Writing – review & editing, Supervision.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper

Acknowledgements

Not applicable.

Abbreviations

CAA	cancer-associated adipocyte
TME	tumor environment
IL-6	interleukin-6
IL-8	interleukin-8
IL-1β	interleukin-1 beta
CCL5	C–C motif chemokine ligand 5
CCL2	C–C motif chemokine ligand 2
VEGF	vascular endothelial growth factor
G-CSF	granulocyte colony-stimulating factor
IGF-1	insulin-like growth factor-1
IGFBP	insulin-like growth factor binding protein
ECM	extracellular matrix
EMT	epithelial-to-mesenchymal transition
WAT	white adipose tissue
BAT	brown adipose tissue
TNF-α	tumor necrosis factor-alpha
FFAs	free fatty acids
CLS	crown-like structure
OSM	oncostatin M
LIF	leukemia inhibitory factor
STAT3	signal transducer and activator of transcription 3
CXCLs	C-X-C motif ligands
IFN-β	interferon beta
TNBC	triple-negative breast cancer
JAK/STAT	janus kinase/signal transducer and activator of transcription
MAPK	mitogen-activated protein kinase
OS	overall survival
ANGPTL4	angiopoietin-like 4
NF-κB	nuclear factor-kappa B
JNK	c-Jun N-terminal kinase
MMP	matrix metalloproteinases
MCF-7	Michigan Cancer Foundation-7
GM-CSF	granulocyte-macrophage colony-stimulating factor
MDSC	myeloid-derived suppressor cell
PLOD2	procollagen-lysine,2-oxyglutarate,5-dioxygenase 2
PI3K/AKT	phosphatidylinositol 3 kinase/protein kinase B

FAs	fatty acids
TIME	tumor immune microenvironment
LFA-1	lymphocyte function-associated antigen 1
TAMs	tumor-associated macrophages
NETs	neutrophil extracellular traps
MEK	mitogen-activated protein kinase kinase
ERK	extracellular regulated protein kinase 1/2
AFG	autologous fat graft
ADSCs	adipose-derived stem cells
LRR	locoregional recurrence
ER	estrogen receptor
EVs	extracellular vesicles
DOX	doxorubicin
FGF1	fibroblast growth factor 1

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