Review

New Insights into Extracellular Vesicles between Adipocytes and Breast Cancer Orchestrating Tumor Progression

Jing Cui[1], Weida Shen[1], Haiyan Zhao[1],*

[1]Department of Breast Surgery, Shanghai Changning Maternity and Infant Health Hospital, East China Normal University, 200062 Shanghai, China
*Correspondence: healthybonheur@163.com (Haiyan Zhao)
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Abstract

In recent years, obesity has been widely considered an independent risk factor for diseases/disorders including inflammation, cardiovascular disease, and cancer. Adipocytes separate in diverse types of tissues, playing vital roles in not only homeostasis but also disease progression. Adipose tissue is not only an energy organ but is also an endocrine organ that can communicate with other cells in the microenvironment. In this review, we assess the functions of breast cancer-associated adipose tissue-derived extracellular vesicles (EVs) in the progression of breast cancer including proliferation, metastasis, drug resistance, and immune regulation. A better understanding of the role of EVs in the crosstalk between adipocytes and breast cancer will provide an understanding of the cancer biology and progression, which would further drive improvements of diagnostic strategies as well as therapeutic insights.

Keywords: extracellular vesicles; adipose; breast cancer; progression; crosstalk

1. Background

Obesity is becoming an intractable problem worldwide as it is viewed as a major driving factor in diverse disorders including some malignancies [1]. An increasing number of studies have focused on cancer-associated adipocytes (CAAs) to evaluate their effects on breast cancer progression [2,3]. Obesity is a chronic inflammatory condition that strongly impacts the progression of breast cancer [4]. In obesity, the breast cancer microenvironment produces extracellular vesicles (EVs) capable of reprogramming breast cancer cells to grow faster and be more aggressive [5]. In addition, obesity causes breast cancer to grow more aggressively by shrewing the breast microenvironment through EVs [6]. EVs, as a type of nanocarrier that deliver encapsulated cargos, can link the crosstalk between CAAs and breast cancer cells. How EVs play roles in breast cancer progression, including metastasis, drug resistance, and immune regulation, are still unclear. In this review, we explore the relationship between breast CAAs and breast cancer, focusing on the newest roles of EVs in breast cancer progression.

2. Breast Cancer

Breast cancer is one of the most common types of cancer in women, affecting more than two million women worldwide annually and accounting for approximately 15% of all cancer-related deaths [7]. Although there are many pre-clinical and clinical studies on targeted combination therapies against breast cancers, breast cancer still poses a great threat to women's health. The factors related to breast cancer progression vary widely from race to diverse lifestyles. In addition, obesity-related metabolic reprogramming is a vital risk factor in promoting breast

cancer [8]. Metastatic relapse and drug resistance remain major challenges in clinical practice despite great advances in breast cancer treatment. Thus, understanding the mechanisms of metastasis and resistance are of significance for future treatments. While the breast cancer tumor microenvironment (TME) contains diverse cell types [9] including cancer-associated fibroblasts, cancer-associated macrophages, vascular endothelial cells, and CAAs, the understanding of crosstalk in the TME is unclear [10]. In recent years, increasing evidence has shown the vital role of environmental exposure in the progression of breast cancer, especially adipocyte tissue [11].

3. CAA Tissue

Adipose tissue can be classified into three major types: brown, white, and beige. Adipose tissues are the major energy storage sites and endocrine organs in the body. Normal adipocytes can be driven into CAAs in the TME through cytokines or metabolites (e.g., fatty acids, pyruvate, lactate) [12]. The change in white adipose tissue reprogramming in the TME can influence the proliferation and progression of breast cancer. Among the increasing risks related to breast cancer, adipocyte-derived EVs have become the focus [8].

The body's homeostasis depends on the balance between energy intake and consumption [13]. Adipose tissue is an endocrine organ that can secrete various adipokines including leptin and adiponectin to communicate with other tissues or cells. CAAs also play a role in regulating the TME. The crosstalk of diverse cell types in the TME is complex. The communication between adipocytes and other cells in the breast cancer microenvironment is of significance.

4. CAAs

Aberrant adipocytes, especially breast cancer-adjacent CAAs, are found at the invasive front of breast cancer [14]. When comparing CAAs with normal adipocytes, CAAs are smaller than normal adipocytes, with irregular shapes and dispersed lipid droplets. Adipocytes can change into CAAs at the invasive front of breast cancer [14]. On the other hand, breast cancer cells can induce mature adipocytes to transform into CAAs, which have reduced lipid content due to lipolysis and enhanced expression levels of pro-inflammatory cytokines and chemokines [15]. Normally, mature adipocytes and epithelial cells consist of the basement membrane. Breast cancer cells exposed to CAAs can break through the basement membrane. Adipocytes adjacent to breast cancer cells can transform into CAAs, and subsequently play important roles in the progression and metastasis of breast cancer [16]. CAAs can play roles in the procedure including adipokine release and metabolic reprogramming, as well as immune cell recruitment [14]. Adipose tissue secreting C-C motif chemokine ligand 2 (CCL2) can lead to the recruitment of macrophages during the progression of breast cancer [17]. Also, CAAs can secrete CCL5, interleukin 1 beta (IL-1β), IL-6, tumor necrosis factor alpha, vascular endothelial growth factor (VEGF), and leptin, which play roles in breast cancer metastasis.

5. EVs

EVs are small membrane vesicular structures derived from diverse cell types including exosomes, macrovesicles, and apoptotic bodies. EVs are released during different cell physiological processes such as senescence or programmed cell death including apoptosis, necroptosis, and pyroptosis. EVs derived from diverse cells can exert diverse functions. For example, EVs derived from stem cells can play roles in wound healing [18], and cancer cell EVs can play roles in developing metastatic niches. EVs have been defined as carrier in cell communications and in modulation of cell biology [19]. In addition, EV-microRNAs (miRNAs) can induce tumor initiation as well as metastasis. Adipocyte-derived EVs play critical roles in regulating metabolic disorders and cancer progression. EVs have also been recognized as potential diagnostic and prognostic biomarkers [20]. Meanwhile, EVs are also promising therapeutic carriers in drug delivery strategies.

6. EVs in Crosstalk between Breast Cancer and Adipose Tissue

6.1 Adipocyte EVs in Regulating Proliferation and Metastasis in Breast Cancer

Among the complex TME in breast cancer, adipocytes play vital roles in tumor progression. Adipocytes surrounding breast cancer secrete numerous EVs to interplay with breast cancer cells and other cell types. EVs derived from mesenchymal stem cell-derived adipocytes can acti-

vate the Hippo signaling pathway [21], and subsequently promote the proliferation of breast cancer cells. In addition, it has been reported that CAA-derived EVs induce hypoxia inducible factor 1 alpha activity in breast cancer cells, and subsequently enhance the invasiveness of breast cancer cells *in vitro* and *in vivo* [21]. Adipose tissues can influence the progression of breast cancer cells by EVs and breast cancer cells can affect the status of adipocytes. EVs derived from cancer cells can interplay with CAAs. Breast cancer EVs can induce the differentiation of adipocytes. Adipocytes can be converted into myofibroblasts by enhancing the expression of VEGF [22]. Also, breast cancer cells can secrete EVs containing miRNA-144 or miRNA-126, which lead to beige differentiation and remodel metabolism in adipocytes [23]. In return, remodeled adipocytes induce tumor proliferation in breast cancer. Thus, the interplay between breast cancer and CAAs forms a type of mutually reinforcing cycle in cancer metastasis.

EVs are a type of nanocarrier for molecules and can encapsulate these cargoes from the original cells, including cargo selection and intraluminal vesicle budding into multivesicular bodies. These require the Endosomal Sorting Complex Required for Transport, lipids, and tetraspanins. The functions of the delivered cargoes have been reported by many groups, but the mechanisms underlying the sorting procedure in the original cells remain unclear. Adipocyte-derived EVs can deliver miRNAs to target cells to further regulate their condition. Adipocyte-derived EV-encapsulated miR-4429 and miR-23b can dysregulate members of the transforming growth factor beta family in hepatic stellate cells and the HepG2 hepatocellular carcinoma (HCC) cells [24] (Table 1, Ref. [24–28]). Also, adipocyte-derived EV-encapsulated miR-140 can increase the migration of breast cancer cells and promote the progression of the cancer [25]. In addition, adipocyte-derived EV-encapsulated circ-BD can promote HCC via activation of the ubiquitin-specific peptidase 7/cyclin A2 axis [26].

6.2 Adipocyte EVs in Regulating Thermotherapy Resistance in Breast Cancer

A growing number of clinical studies have reported that obesity can increase the invasiveness of breast cancer. CAAs are linked to chemotherapy resistance and tumor progression. One study has shown that when breast cancer cells are cultured with adipocyte conditioned medium, the breast cancer cells become resistant to lapatinib [29], possibly because EVs derived from adipose tissue can lead to drug resistance. One study has cultured breast cancer cells with adipose tissue-derived EVs and the treated breast cancer cells underwent proliferation [29]. In the breast cancer microenvironment, CAAs can induce breast cancer cells to transform into a multidrug-resistant cancer cell phenotype by promoting the high expression of transport-associated major vault proteins [30]. In addition, adipose stem cells can induce radiation resistance

Table 1. Adipocyte-derived EV miRNAs and cancer.

EV miRNAs	Regulation targets	Related mechanism	Citation
miR-4429	HCC	Dysregulates TGF-β family members	[24]
miR-23b	HCC	Dysregulates TGF-β	[24]
miR-23a/b	HCC	Downregulation of VHL	[27]
miR-140	Breast cancer	Increases migration	[25]
miR-4792	Ovarian cancer	Influences apoptosis	[28]
miR-320b	Ovarian cancer	Influences apoptosis	[28]
circ-BD (circRNA)	HCC	Activation of USP7/cyclin A2	[26]

miRNA, microRNA; circ-BD, circRNA-BD; HCC, Hepatocellular carcinoma; TGF-β, Transforming growth factor beta; VHL, von Hippel–Lindau; USP7, ubiquitin-specific peptidase 7.

in breast cancer [31]. However, adipocyte-derived EVs could be a promising drug delivery system for breast cancer treatment. Adipose-derived mesenchymal stem cells-derived EVs can be used as a nanocarrier to deliver miRNA-1236, which can reduce cisplatin resistance in breast cancer [32]. Another study has shown that EVs collected from the adipocytes of patients with multiple myeloma (MM) can protect MM cells from chemotherapy-induced apoptosis by enhancing methyltransferase-like protein 7A activity [33]. Thus, CAA-derived EVs can regulate the microenvironment of diverse cancers, and further regulate the thermotherapy sensitivity and outcome of diverse thermotherapies.

6.3 Adipocyte-Derived EVs in Immune and Metabolic Regulation in Breast Cancer

There are diverse cell types in the breast cancer microenvironment including cancer cells, CAAs, immune cells, and cancer-associated fibroblasts. Crosstalk between CAAs and immune cells is of significance to regulate the balance of the TME and cancer progression. Tumor-associated macrophages (TAMs) play roles in tumor progression [34]. TAMs can induce tumor progression by mediating the processes of angiogenesis and immunosuppression among others [35]. Adipose tissue is the primary source of many proinflammatory cytokines in the microenvironment. The number of macrophages and phenotype (proinflammatory or non-proinflammatory) are associated with adipocyte tissues [36]. CAAs are a vital immunomodulatory factor in the TME. The expression of programmed death-ligand 1 in CAAs can inhibit the antitumor effects of CD8+ T cells [37]. In addition to immune regulation, CAAs also regulate metabolic processes in the breast cancer microenvironment. Some studies have reported that adipocyte-derived EVs can induce the expression of genes associated with the epithelial-to-mesenchymal transition (EMT) and cancer stem-like cell traits in breast cancer in type 2 diabetes, possibly because ATP released from CAAs can regulate the immune microenvironment and facilitate breast cancer progression [38]. EVs encapsulating miR-NAs and long noncoding RNAs play roles in regulating the pathological processes of diabetes, including the me-

diation of metabolic signals as well as inflammatory pancreatic cells [39]. In addition, EVs produced by metabolically abnormal adipocytes can mediate the progression of breast cancer. A cohort study showed that EV proteins from insulin-resistant adipocytes are associated with the EMT and cancer stem cells (CSCs) among breast cancer patients [38]. Another group reported that EVs derived from preadipocytes can mediate the stemness of breast CSCs as well as the migration ability of breast cancer cells through the miR-140/SRY-box 2 (SOX2)/SOX9 axis [25]. Therefore, adipocyte-derived EVs can induce the metabolic reprograming of breast cancer cells and subsequently promote aggressive phenotypes in breast cancer.

6.4 Applications of EVs in Breast Cancer

Over the last decade, the field of EVs has grown tremendously, offering tremendous potential for clinical diagnosis and therapeutic applications. While EVs are a heterogeneous group of nanoparticles acting as mediators of many pathological and physiological processes, they are also being explored for drug delivery due to their intrinsic tissue-homing capabilities. A group from China reported that chemotherapy-elicited EVs miR-378a-3p and miR-378d can promote the stemness and chemoresistance of breast cancer by activating the enhancer of zeste homolog 2/signal transducer and activator of transcription 3 pathway [40]. Frederic St-Denis-Bissonnette reported that EVs from MDA-MB-231 triple-negative breast cancer can deliver doxycycline with decreased cardiac toxicity [41]. This group also reported that ovarian cancer-associated EVs have the same ability [42]. On the other hand, not only inside cargoes can be applied against breast cancer, but also the displaying ligand can also be applied to inhibit the development of breast cancer. A group from the United States reported that EVs displaying the epidermal growth factor receptor (EGFR) aptamer can inhibit orthotopic breast cancer models. When the EGFR aptamer is displayed on the surface of EVs, the uptake of EVs is enhanced due to the tumor-targeting capabilities *in vivo* (treatment with EGFR-labeled EVs at a dose of 0.5 mg can significantly inhibit tumor growth) [43].
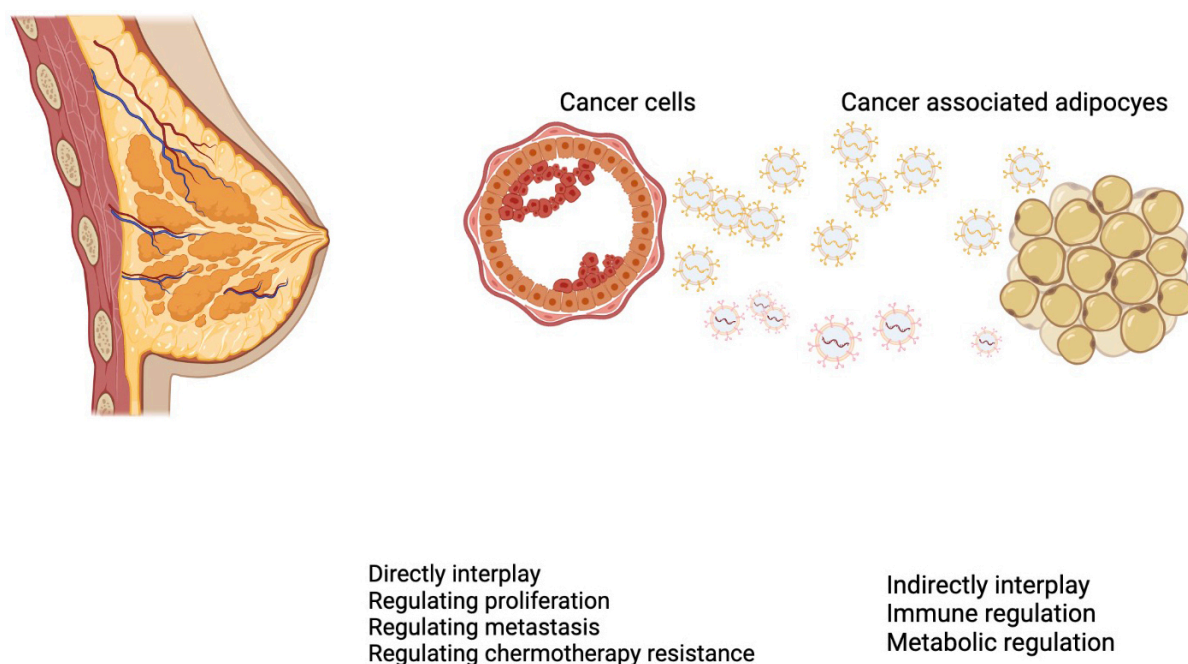
Fig. 1. EVs mediate the interplay between adipocytes and breast cancer.

7. Summary and Perspectives

Breast cancer has become a leading cause of cancer-related death among women worldwide [41]. We reviewed the CAA-derived EVs and their functions in the progression of breast cancer including cancer proliferation, cancer metastasis, drug resistance, immune regulation, and metabolic regulation (Fig. 1). While adipose tissues are regarded as key regulator in breast cancer progression, the underlying regulatory mechanism is unclear. The effects of adipose tissue-derived EVs on the hallmarks of cancer are critical for tumor malignancy [44]. In this review, we focus on the mechanism of EVs in the crosstalk and interplay between adipocytes and cancer cells, rather than only the hallmarks of cancer. Obesity is becoming a pandemic in some developing countries, and is now considered a risk factor for cancer progression. Obesity systemically preconditions the TME for future metastasis by favoring the formation of proinflammatory niches and regulating tumor cells [45]. In the present review, we highlighted the roles of EVs in the crosstalk and interplay between adipocytes and cancer cells, as well as between adipocytes and other cell types in the breast cancer microenvironment. Although there are increasing studies on adipose tissue-derived EVs, more studies are needed to reveal the underlying mechanisms and specific signaling, which promote the applications of fat-derived EVs from the bench to the bedside. It is well acknowledged that CAAs can orchestrate the progression of breast cancer through EVs.

Author Contributions

JC, WS and HZ designed, wrote and revised the manuscript, and JC was a major contributor in writing the manuscript and prepared the figure. WS also participated in the analysing data of the manuscript. JC and WS made significant revisions and proofread the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of Interest

The authors declare no conflict of interest.

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