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Review

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The role of miRNAs in the extracellular vesicle-mediated interplay between breast tumor cells and cancer-associated fibroblasts

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Abstract

The tumor microenvironment (TME) of breast cancer (BC) is depicted as an immunosuppressive dwelling that comprises a myriad of cell types embedded in the extracellular matrix. As one of the most abundant cell populations within the TME, cancer-associated fibroblasts (CAFs) play indispensable roles in increasing cancer aggressiveness and promoting resistance to standard-of-care therapies. Extracellular vesicles (EVs) represent a diverse array of biological nanoparticles, encompassing exosomes, microvesicles, and apoptotic bodies. In recent years, these cell-derived membranous structures have raised great interest as they can encapsulate numerous types of cellular cargo, such as proteins, lipids, and miRNAs. By transmitting bioactive content to recipient cells, EVs play pivotal roles in intercellular communication between CAFs and tumor cells. EVs secreted from tumor cells typically activate resident fibroblasts to acquire a myofibroblastic phenotype, while EVs diffused by CAFs, in turn, substantially increase the progression of BC. This review summarizes the latest findings to highlight the functional

role of EV cargo, especially miRNAs, in the regulatory network. A better understanding of the EV-mediated cell-cell interactions is crucial to achieving effective treatment in patients with BC.

Keywords: Cancer-associated fibroblast, extracellular vesicles, tumor microenvironment, intercellular communication, breast cancer

INTRODUCTIONS

According to the latest global cancer statistics, breast cancer (BC) is the most commonly diagnosed cancer in women, with approximately 2.3 million new cases in 2022[1]. Although much effort has been invested in improving the prognosis of patients in recent decades, BC continues to be one of the main causes of tumor-associated death in women[2]. The current treatment methods for BC are primarily surgery, radiotherapy, chemotherapy, endocrine therapy, and targeted therapy[3]. However, the immunosuppressive cells surrounding the tumor greatly limit the therapeutic efficacy and promote the progression of cancer[4].

The tumor microenvironment (TME), which is of vital significance in influencing the conditions that impact tumor development and progression, refers to the noncancerous elements in the vicinity of tumor cells, such as immune cells, stromal cells, the extracellular matrix (ECM), and signaling molecules produced by these various cells[5]. As a key component of the TME, cancer-associated fibroblasts (CAFs) exhibit a spindle-shaped morphology with irregular nuclei and abundant cytoplasm. Compared with normal fibroblasts (NFs), CAFs demonstrate increased activity levels and produce greater amounts of cytokines and immunomodulatory factors, thus modulating the TME and influencing tumor growth, angiogenesis, and metastasis[6]. Recent studies revealed that the intercellular communication between neoplastic cells and surrounding CAFs is not only based on ECM remodeling but also modulated by paracrine signals[7]. CAFs stimulate the survival and self-renewal programs of cancer cells, which increases their motility and promotes the metastasis of malignant cells[8].

Extracellular vesicles (EVs) are membranous vesicles that can be produced in response to various stimuli and are widely distributed in tissue fluids, such as human blood, lymph fluid, cerebrospinal fluid, urine, and saliva[9]. These cell-derived membranous structures can diffuse from a vast majority of eukaryotic cell types both under physiological conditions and during pathological processes[10]. According to studies on the formation processes of EVs, these vesicles can generally be classified into three main categories: exosomes, microvesicles, and apoptotic bodies. Exosomes typically originate through inward budding of the endosomal membrane and are released after the fusion of multivesicular endosomes (MVEs) with the cell membrane. Microvesicles are produced via outward budding of the plasma membrane, after which they are secreted into the extracellular environment[11]. On the other hand, apoptotic bodies are vesicles produced by the plasma membrane during cell disintegration as a result of programmed cell death[9]. EVs are capable of transporting proteins, lipids, and nucleic acids and act on recipient cells in a paracrine or endocrine manner, thereby affecting the physiological functions and phenotypes of the recipient cells[12]. These vesicles also play essential roles in multiple pathological conditions. For example, EVs can transfer chemotherapeutic agents out of cancer cells, leading to increased drug resistance in malignant tumors[13].

In recent decades, emerging evidence has shown that EVs secreted by CAFs can regulate tumor proliferation and migration through complex signaling networks; correspondingly, EVs secreted by tumor cells can induce the differentiation of NFs into CAFs, thus creating a specific microenvironment favorable for tumor growth[6]. Therapeutic strategies targeting EVs have become a promising direction in the research field of BC treatment. Here, to deepen the understanding of EV-based bidirectional signal transduction, we

systematically summarized the interplay between CAFs and BC cells from tumorigenesis to tumor metastasis. Moreover, EV-related therapeutic approaches for the diagnosis and treatment of BC are also summarized in this review.

THE PATHOLOGICAL ROLE OF CAFs

The TME is mainly composed of tumor cells, stromal cells, and the extracellular matrix (ECM), among which stromal cells primarily include fibroblasts, immune cells, and endovascular cells[14]. As a prominent component of stromal cells in the TME, CAFs are identified by the presence of activation biomarkers, including α-smooth muscle actin (α-SMA) and fibroblast activation protein (FAP), along with a variety of secreted factors that are interrelated with ECM remodeling and immune infiltration[15].

The origin of CAFs

Currently, although the precise origin of CAFs has yet to be elucidated, evidence has shown that CAFs are derived from a wide range of sources. CAFs mainly originate from local resident fibroblasts and stellate cells, which can be activated by pathological stimulation. For example, quiescent stellate cells can acquire a myofibroblast-like phenotype and transcriptional features under the influence of inflammatory factors[16,17]. In addition, CAFs can arise from bone marrow-derived mesenchymal stem cells (BM-MSCs). Barcellos-de-Souza *et al*. reported the transforming growth factor-beta (TGF-β)-mediated differentiation of MSCs into CAF-like cells, which play a crucial role in promoting tumor invasiveness[18]. Additionally, epithelial and endothelial cells can also differentiate into CAFs via transformation through epithelial-mesenchymal transition (EMT) or endothelial-mesenchymal transition (EndMT)[19,20]. Furthermore, some studies have shown that adipocytes, pericytes, and smooth muscle cells are also relevant to the formation of CAFs[21]. These diverse origins of CAFs underscore the complex nature of their involvement in tumor progression and highlight the need for further research to better understand their role in cancer development.

Subpopulations of CAFs

The diverse origins of CAFs lead to their phenotypic heterogeneity; thus, CAFs generate a variety of markers, such as α-SMA, FAP, fibroblast-specific protein-1 (FSP-1), S100A4, platelet-derived growth factor receptor (PDGFR), and vimentin (VIM)[22]. However, these markers lack specificity because they are not exclusively expressed by CAFs and can be detected in other healthy tissues. The increasing discovery of various subtypes of CAFs highlights the need for a more precise classification system to effectively guide therapeutic strategies targeting CAFs[23].

Research has revealed that two distinct subpopulations of CAFs were present in virtually all types of cancers: myofibroblastic CAFs (myCAFs), which are characterized by elevated levels of α-SMA expression, and inflammatory CAFs (iCAFs), which do not express α-SMA but instead secrete IL6[24,25]. MyCAFs are found adjacent to cancer cells and can produce ECM components and remodel the ECM, while iCAFs are located distant from tumor cells within the stroma and express high levels of cytokines and chemokines[26].

CAFs have been reported to arise from NFs that reside in the breast tissue of invasive lobular BC patients, among which $CD26^+$ NFs are converted to protumorigenic iCAFs. These iCAFs play crucial roles in recruiting myeloid cells in a CXCL12-dependent manner. Additionally, they contribute to increasing the invasive ability of malignant tumor cells via increasing matrix metalloproteinase (MMP) activity[27]. Notably, the myCAF and iCAF subpopulations can be interconverted through specific signaling pathways[21]. These findings suggest that manipulating the subtypes of CAFs may hinder the growth and invasion of malignant tumors, offering valuable insights for cancer treatment.

Through single-cell RNA sequencing (scRNA-seq), researchers have identified a new subtype of CAF that expresses major histocompatibility complex (MHC) class II and CD74 but lacks expression of classical costimulatory molecules. These cells were defined as "antigen-presenting CAFs" (apCAFs). ApCAFs are capable of inducing $CD4^+$ T cell activation in an antigen-specific fashion. Interestingly, two-dimensional (2D)-cultured apCAFs lost MHCII expression but upregulated myCAF markers, further confirming that subpopulations of CAFs are interconvertible[28]. By applying scRNA-seq, other rare subtypes of CAFs have been discovered, such as vascular CAFs (vCAFs), cycling CAFs (cCAFs), developmental CAFs (dCAFs), and matrix CAFs (mCAFs)[29]. Given the discrepancies in the classification of CAFs, in this review, we focused on the universal characteristics of CAFs rather than specific subgroups.

BIOGENESIS AND SUBPOPULATIONS OF EVs

EVs are cell-derived spherical particles enclosed by a phospholipid bilayer[30]. These lipid-membrane-bound vesicles typically range from 30 nm to 5 μm in size and carry a wide spectrum of cell-released biomolecules (e.g., proteins, metabolites, and nucleic acids)[31]. Under certain circumstances, they can also contain subcellular organelles such as mitochondria[32]. Malignant cells have recently been shown to release more EVs than normal neighboring cell types do, and they can be detected in bodily fluids, making them promising diagnostic and prognostic biomarkers for cancer treatment[33].

According to their biogenesis pathways, EVs can be categorized into three classic subtypes: exosomes, microvesicles, and apoptotic bodies[34]. The generation process and biological features vary distinctly among these subpopulations. Exosomes and microvesicles exhibit constitutive and inducible expression from a vast number of eukaryotes and show remarkable potential as blood-based or urine-based indicators for cancer patients, whereas apoptotic bodies partially reflect the prevalence and cellular composition of dying cells[35].

Exosomes

Exosomes (30-200 nm) are the smallest type of EVs with an endosomal origin[36,37]. The biogenesis of exosomes occurs through the inward growth of the plasma membrane and the generation of multivesicular bodies (MVBs) carrying intraluminal vesicles (ILVs)[38]. In the initiation stage of exosomes, the invaginated plasma membrane forms a cup-like structure housing cell-surface proteins and soluble proteins associated with the extracellular space[38,39]. The endosomal membrane subsequently generates an intraluminal budding process toward the lumen to create MVBs[40]. These endocytic structures end up in the cell in two ways, either merging with lysosomes or autophagosomes for degradation or integrating with the outer cell membrane, resulting in the secretion of the contained ILVs, commonly known as exosomes, into the ECM[38,41]. These vesicles can travel freely in body fluids to transmit information in autocrine, paracrine, or endocrine manners, thus modulating the biological behavior of target cells[42,43]. In pathological states, such as cancer, the dysregulation of exosomes has been found to be associated with the clinical features and survival outcomes of patients[44]. It was reported that the endogenously expressed protein TRIM1-269aa could be packed into exosomes, thus activating the PI3K/AKT/mTOR pathway and promoting the chemoresistance and metastasis of triple-negative breast cancer (TNBC)[45].

Microvesicles

Microvesicles (also referred to as ectosomes or microparticles) are apparently larger than exosomes[46]. Both exosomes and microvesicles are composed of a lipid bilayer membrane-enclosed structure, which protects the contents from degradation and potential environmental threats[11]. However, unlike exosomes, microvesicles are directly formed by outward budding and fission of the plasma membrane, followed by the instantaneous secretion of vesicles into the intercellular milieu[47]. To the best of our knowledge, the formation of microvesicles basically includes four stages: intracellular Ca^{2+} mobilization, remodeling of the

actin cytoskeleton, kinase phosphorylation, and NF-κB activation[48]. Because they belong to distinct subsets of EVs, submicron-sized microvesicles have not attracted as much attention as exosomes have. However, in recent decades, there have been profound changes in our understanding of these particles[49]. Microvesicles have been shown to have a significant effect on various pathological processes, including vascular inflammation and aberrant angiogenesis[50,51]. Majno *et al.* reported that tumor-derived microvesicles play an essential role in regulating the differentiation of monocytes in the TME[52]. Moreover, the functions of $CD8^+$ T cells are strongly disrupted by microvesicle-shuttled PD-L1, which leads to a suppressive TME in TNBC patients[51].

Apoptotic bodies

Apoptotic bodies are a special subset of EVs that are generated from cells undergoing programmed cell death[53]. These vesicles are shown to have structures and phenotypic properties comparable to those of exosomes and microvesicles[35]. However, because of the lysis of apoptotic cells, the size and composition of apoptotic bodies vary, making it more difficult to establish common standards for investigation[54]. The formation of apoptotic bodies begins with cell shrinkage, nuclear chromatin condensation and internucleosomal fragmentation of genomic DNA, followed by extensive membrane ruffling and blebbing, leading to disintegration of the cellular content into separate membrane-encapsuled vesicles[55]. Once secreted into the extracellular space, similar to other subtypes of EVs, apoptotic bodies can also strongly regulate target cells by releasing their composition, such as histones, organelles, and DNA fragments[56]. According to Yin *et al.*, apoptosis induced by Photodynamic therapy and chemodynamic therapy could generate δ-ALA-containing apoptotic bodies, which further facilitate tumor-killing effects in deep malignant cells[57]. Moreover, these vesicles showed distinct advantages in the application of nanomedicine systems. Using apoptotic bodies and Ti_2N nanosheets, Yang *et al.* reported a new drug delivery system (Ti_2N-DOX@ABs), which exhibits a high drug loading capacity[58].

On the basis of these three canonical subtypes, technological advances have further enabled more precise classification of these particles, such as matrix vesicles, migrasomes, and large oncosomes[59]. Nevertheless, separating multiple subpopulations of EVs is still challenging because reliable biomarkers are lacking. Therefore, the general term EV was adopted in most published articles.

CANCER-DERIVED EVs DICTATE PREFERABLE CAF CHARACTERISTICS FOR BC PROGRESSION

During the development and progression of a neoplasm, various cells, such as MSCs and macrophages, migrate into the stromal microenvironment in response to the recruiting effects of tumor cells, whereas fibroblasts typically populate both primary and distant lesions[60]. These cells within the TME are "reeducated" by malignant cells and subsequently acquire protumoral activities[60,61]. In summary, the cancer immunoediting process comprises three phases: tumor elimination, tumor dormancy, and tumor escape from immune surveillance[62]. As important factors involved in the interplay between tumor cells and nontumor cells, EVs significantly influence different stages of tumor progression, including angiogenesis, cell migration, tumor-associated immune modulation, and TME remodeling[63]. According to Li *et al.*, tumor-derived miR-770 can be translocated to tumor-associated macrophages (TAMs) via exosomes, thereby mediating immune remodeling and drug resistance in TNBC cells[64]. Consistently, emerging evidence has shown that fibroblasts can also communicate with cancer cells via EVs to acquire a specific phenotype. As shown in Table 1, BC-derived EVs could effectively influence various biological processes in surrounding CAFs.

Table 1. The role of cargos in BC-derived EVs on CAFs

Cargo	Target	Impact on CAFs	PMID
FN and Ttg	Mitogenic signaling pathway	Cellular transformation	21368175
miR-122	PKM2 and GLUT1	Suppress glucose uptake	25621950
miR-9	EFEMP1, MMP1, COL1A1	Fibroblast activation	27468688
TGF-β	MAPK signaling pathway	Myofibroblastic differentiation	27913195
miR-105	MYC signaling pathway	Promote glucose and glutamine metabolism	29662176
miR-125b	TP53 and TP53INP1	Fibroblast activation	31044053
ITGB4	BNIP3L	Promote aerobic glycolysis	31534187
miR-146a	TXNIP	Fibroblast activation	32268136
Survivin	SOD1	Myofibroblastic differentiation	32709750
miR-105 and miR-204	RAGC	Suppress amino-acid-induced protein synthesis	33345445
miR-370-3p	CYLD/NF-κB signaling pathway	Fibroblast activation	33629796
Integrin αvβ1	-	Fibroblast activation	35923105
miR-130b-3p	SPIN90	Fibroblast activation	35948548
NME1 and NME2	FASN, ACSS2	Suppress fatty acid synthesis	36010906
Tg2	FAK signaling pathway	Fibroblast activation	36475545

In 2014, Papi *et al.* proposed that exosomes released by BC cells under hypoxic conditions stimulate mammary gland fibroblasts into a proinflammatory phenotype[65]. Additionally, Jung *et al.* reported that tumor cells substantially increase the production of ECM fibrils in the early stage of BC, which facilitates the secretion of EVs that shuttle CAF-promoting molecules[66]. Adipose-derived stem cells (ASCs) treated with EVs released from BC cells subsequently undergo differentiation into myofibroblasts, with high expression of α-SMA and activation of TGF-β-associated signaling networks[67]. Moreover, EVs secreted from distinct subpopulations of tumor cells have been demonstrated to have different effects on CAFs. As reported by González-Callejo *et al.*, cancer stem cell (CSC)-derived EVs can efficiently switch CAFs into a myofibroblastic phenotype, whereas EVs from nonstem cells stimulate secretory CAFs to help CSCs maintain stemness via the IL-6/IL-8 signaling pathway[68].

The transglutaminase family comprises versatile molecules with enzymatic and scaffolding functions that are involved in the modulation of cell destiny in numerous cellular systems and have been demonstrated to be crucial players in various pathological processes[69]. A decade ago, scientists demonstrated that BC-derived tissue transglutaminase transmitted by microvesicles was tightly associated with mitogenic signaling activities and fibroblast transformation[70]. It was further proposed by Schwager *et al.* that tissue transglutaminase 2-rich microvesicles could effectively stimulate fibroblasts into CAFs[71], thereby augmenting the migration of BC cells in the TME. Survivin (also known as BIRC5), which is highly expressed in neoplastic tissue[72,73], was reported to be intimately correlated with poor survival rates in multiple malignancies[72]. EV-encapsulated survivin derived from BC could be received by surrounding stromal cells and effectively promote their transdifferentiation into a myofibroblastic state[74].

MicroRNAs (miRNAs) are small endogenous RNAs that typically range from 18 to 25 nucleotides in length[75]. In 1993, the first miRNAs were discovered by Lee *et al.* in *C. elegans*[76]. Since then, many miRNAs have been found in a broad range of organisms[77]. Primary miRNAs (pri-miRNAs) are generated from RNA polymerase II/III-specific transcripts in the nucleus to form a hairpin structure[78]. A heterotrimeric complex microprocessor, which is composed of DROSHA and its cofactor DGCR8, subsequently cleaves the local hairpin structures into ~70-nucleotide small stem loops[79]. After being exported into the cytoplasm, the loop is cleaved by RNase III Dicer, thereby forming a double-stranded structure of miRNA and antisense

miRNA[80]. The latter is typically degraded, whereas the other strand guides the miRNA-induced silencing complex (miRISC) to partially complementary sequences in target mRNAs for degradation and translational suppression[81,82]. MiRNAs are involved in multiple biological processes in cancer, such as cell apoptosis, migration, and angiogenesis, and also serve as biomarkers for cancer diagnosis and assessment of prognosis. Recently, emerging evidence has shown that miRNAs also play a functional role in EV-based intercellular crosstalk.

Recently, increasing evidence has suggested that EV-encapsulated miRNAs, such as miR-370-3p[83], miR-9[84], miR-130b-3p[85], miR-146a[86], miR-125b[87], miR-204[88], and miR-105[88,89] which are secreted from BC cells, are responsible for fibroblast activation. Furthermore, the synergistic action of tumor-derived exosomal miRNAs, miR-185-5p, miR-652-5p, and miR-1246, was shown to enhance the mobility and contraction of fibroblasts in the TME, which facilitates the differentiation of CAFs toward a promigratory phenotype[90].

CAFs can undergo energy metabolism reprogramming under specific circumstances, thus influencing the aggressiveness of surrounding tumor cells[91]. Integrin beta4 (ITGB4) can be released by TNBC cells through exosomes, which then induces BNIP3L-dependent mitophagy and lactate generation in CAFs[92]. Tumor-released miRNAs, such as miR-105 and miR-122, have also been shown to be key players in the regulatory mechanism of glycolysis in fibroblasts[89,93]. In addition, an association was found between tumor-derived EVs and lipid metabolism in CAFs. Fibroblasts treated with NME1/2 protein-containing EVs presented markedly lower expression of genes associated with fatty acid and cholesterol metabolism[94].

CAF-DERIVED EVs CONFER MALIGNANT PROPERTIES ON BC CELLS

As the dominant cell population in the TME, CAFs are known to be pivotal for mediating cancer progression and drug resistance via deposition of the ECM[95]. The dense ECM in solid tumors significantly abrogates the penetration of therapeutic agents, thus substantially impairing the therapeutic results[96]. Recent research revealed that EVs can transmit various kinds of factors inherited from their parent cells, which also play an indispensable role in such cell-cell interactions. As shown in Table 2, CAF-derived EVs could significantly regulate the malignant behavior and the gene expression profiles in BC cells.

Proliferation, migration, and invasion

Recent studies have highlighted the significant impact of metastasis on the prognosis of patients with malignant tumors, with CAFs identified as key players in promoting metastasis across various cancer types. Luga *et al.* reported that stromal exosomes could considerably facilitate the protrusive activity and cell migration in BC through the Wnt-PCP signaling pathway[97]. Chen *et al.* reported that p85a-deficient CAFs could markedly augment BC progression through exosomal Wnt10b in a paracrine manner[98]. Upregulated Wnt10b in tumor cells led to activation of the Wnt/β-catenin signaling pathway, which efficiently induced the metastasis of tumor cells via EMT. Hypoxic CAFs secrete exosomes rich in the protein GPR64, which triggers the noncanonical NF-κB pathway to facilitate the expression of MMP9 and IL-8 in recipient BC cells, thereby increasing cell migration and invasion[99]. Furthermore, ADAM10-enriched exosomes secreted by CAFs were shown to activate the Notch pathway to augment the expression of aldehyde dehydrogenase and remarkably accelerate cancer metastasis by regulating the GTPase RhoA[100].

Recent studies revealed that CAF-released miRNAs also play essential roles in regulating biological processes in cancer cells. miR-4516 secreted by NFs effectively inhibits tumor progression by interacting with the target gene FOSL1. However, CAFs presented markedly lower levels of miR-4516, which resulted in proliferative and migrative features in TNBC cells[101]. Overexpression of miR-214 was found to be highly

Table 2. The effects of molecules in CAF-derived EVs on BC cells

Cargo	Target	Impact on CAFs	PMID
Wnt10b	Wnt/β-catenin pathway	EMT/metastasis	28394344
miR-7641	HIF-1α pathway	Stemness/glycolysis	34238918
miRNA-1-3p	GLIS1	Proliferation/metastasis	33154575
miR-221	ER lo/Notch hi feed-forward loop	Metastases/therapy-resistant	28202520
RN7SL1	PRR, RIG-I	Proliferation/metastasis/therapy resistance	28709002
miRNA-92	LATS2	Proliferation/metastasis	33162971
miR-3613-3p	SOCS2 expression	Proliferation/metastasis	32344463
Cd81	Wnt11	Metastasis	23806092
miR-22	Erα, PTEN	Tamoxifen resistance	33173749
miR-4516	FOSL1	Proliferation	31672492
miR-214	TFAP2C	Metastasis	36639824
miR-16	CCNE1, TWIST1	Metastasis	31988451
miR-148a	WNT1, WNT10B	Metastasis	31988451
CD44v3	ESCRT signaling pathway	Radioresistance/expansion	36106109
miR221/222	MAPK signaling pathway	ER repression	26186233
mtDNA	-	Metabolic changes	29073103
lncRNA SNHG3	miR-330-5p/PKM signaling pathway	Proliferation/metabolic changes	31956955
miR-185-5p	-	Metastasis	35317202
miR-652-5p	-	Metastasis	35317202
miR-1246	-	Metastasis	35317202
miR-181d-5p	CDX2, HOXA5	Proliferation/anti-apoptosis	31955007
miR-500a-5p	USP28	Proliferation/metastasis	33664871
lncRNA H19	miR-497/DNMT1 signaling pathway	Proliferation/metastasis/chemoresistance	38558442
Cd81	Wnt-PCP signaling pathway	Metastasis	23260141
ADAM10	RhoA and Notch signaling pathway	Motility	25150980
circTBPL1	miR-653-5p/TPBG signaling pathway	Proliferation/metastasis	37495592

associated with stromal components, especially CAFs and MSCs, in samples from BC patients. Cancer-mediated activation of IL-6/STAT3 signaling in CAFs led to the accumulation of miR-214-enriched EVs in TME, which subsequently enhanced extravasation and metastasis formation of BC[102]. In coculture systems, miR-181d-5p encapsulated by CAF-derived EVs can be transmitted into MCF-7 cells and directly target the CDX2/HOXA5 signaling pathway by antagonizing apoptosis and promoting EMT in BC[103]. It was revealed by Tao *et al.* that miRNA-1-3p encapsulated by fibroblast-derived EVs could interact with Krüppel-like zinc-finger protein Gli-similar 1 (GLIS1) to inhibit BC growth and migration[104]. The expression level of miR-1-3p was significantly downregulated in CAF-secreted EVs, making it a potential therapeutic target in BC patients. miR-16 and miR-148a reportedly decelerate tumor metastasis, which is markedly suppressed in EVs from CAFs with FAK signaling activation[105]. In addition, according to our previous study, exosomal miR-500a-5p released by CAFs enhances the malignant properties of BC cells via interactions with ubiquitin-specific peptidase 28 (USP28)[106]. On the basis of advances in high-throughput sequencing technologies, more differentially expressed miRNAs have been identified between EVs derived from NFs and those derived from CAFs in BC patients. In the research of Liu *et al.*, a miRNA array revealed that miR-3613-3p was sharply upregulated in CAF exosomes[107]. EV-shuttled miR-3613-3p from CAFs substantially enhanced the proliferative and migrative capabilities of BC cells via direct targeting of the tumor-suppressing gene SOCS2. According to Dou *et al.*, a significantly increased expression level of miR-92 was found in CAF-derived exosomes, which led to the downregulation of the target gene LATS2 in BC cells, thus promoting both the proliferation and migration of cancer cells[108]. Consistently, a recent study further

revealed that these miR-92-containing stromal exosomes could also increase the invasive ability of tumor cells by attenuating the expression of another target gene, G3BP2[109].

Circular RNAs (circRNAs) are single-stranded RNA molecules that are created through back-splicing, resulting in covalently closed loops[110]. Once considered transcription noise, these non-coding RNAs were subsequently shown to be crucial players in the progression of various cancers. Scientists have reported that circRNAs, such as circHIF1A and circRNA-CREIT, can also be packaged into EVs, thus influencing cell-cell communication in BC[111,112]. With respect to tumor-stromal interactions, exosomal circTBPL1 secreted from CAFs could markedly protect TPBG from miRNA-induced degradation by acting as a miR-653-5p sponge, consequently reinforcing the proliferation and metastasis of BC cells[113].

The signal recognition particle (SRP), an ancient ribonucleoprotein machine composed of a 7S RNA and six polypeptides, is crucial for the delivery of secretory and membrane proteins across the endoplasmic reticulum (ER)[114]. SRP RNA plays a fundamental role in SRP assembly, translational elongation stalling, and stimulation of SRP guanosine triphosphatases[115]. In BC, unshielded SRP RNA RN7SL1 covered by stromal EVs could be released into the extracellular space and received by tumor cells, thereby exacerbating cell proliferation and migration by triggering the pattern recognition receptor RIG-I[116].

Metabolic changes

It has been seven decades since Otto Warburg discovered reprogrammed metabolism in malignant cells, which includes increased glucose uptake and increased glycolysis[117]. Alterations in metabolic processes in neoplasms, such as increased cell growth, metastasis and angiogenesis, are interrelated with the phenotypic traits of tumor cells compared with those of normal cells[118]. These distinct metabolic characteristics satisfy the increased energy demand in neoplasms, thus playing a crucial role in the development and progression of cancer[119]. In recent years, emerging evidence has shown that the functional significance of these biological changes in metabolism is not only based on different BC subtypes but also associated with communication between tumor cells and intricate TMEs[120].

A recent study revealed that miR-7641 plays a key role in the regulation of glycolysis by interacting with HIF-1a signaling networks. Compared with that in NFs, a lower expression level of miR-7641 was found in CAF-derived small EVs, which facilitated glycolysis and adjacent stem cell populations in the BC niche[121].

The mechanism of competitive endogenous RNA (ceRNA) activity involves transcripts that possess shared miRNA binding sites engaging in competition for posttranscriptional regulation during the progression of different types of cancer[122]. The CAF-derived lncRNA SNHG3 can be packaged into exosomes and serve as a miR-330-5p sponge after being received by BC cells, thereby protecting PKM from degradation. Upregulated PKM subsequently suppresses mitochondrial oxidative phosphorylation and markedly increases glycolytic carboxylation, which leads to accelerated cancer growth[123].

Therapy resistance

Drug resistance resulting from long-term drug use has emerged as a critical issue in the treatment of malignant tumors. Tumor drug resistance is influenced not only by tumor cells and the neoplasm microenvironment, but also by the role of CAFs, which has become a prominent topic in research. In recent years, scientists have found that EVs played a significant role in CAF-induced therapy resistance. Despite the serious adverse reactions, chemotherapy remains the gold standard for BC treatment[124]. Epirubicin is a widely used anthracycline for BC patients in oncological practice[125]. When stimulated by epirubicin, stressed CAFs can subsequently release exosomes in a TCF12-mediated manner, which increases the

expression of CXCR4 and c-Myc in ER$^+$ BC cells to facilitate treatment resistance to epirubicin[126]. Paclitaxel (PTX) is considered the gold standard chemotherapeutic drug for various malignancies, such as pancreatic cancer and BC[127]. In BC research, Tao *et al.* reported that hypoxia-induced CAFs released lncRNA H19, which could be delivered to surrounding tumor cells via EVs, which led to paclitaxel resistance via regulation of the expression of miR-497[128].

Radiotherapy plays an indispensable part in the recent progress of anti-cancer therapies, including elevation in organ-sparing treatment and achieving lower local recurrence and longer survival time[129]. CAFs triggered by radiotherapy can secrete increased levels of EVs into the TME, which substantially increase the survival of BC cells through exosomal srpRNA RN7SL1 and the expression of the heparan sulfate proteoglycan CD44v3 on the outside membrane of the vesicles[116,130].

Endocrine therapy markedly prolongs overall survival in both pre- and postmenopausal patients with hormone receptor (HR)-positive BC[131]. However, the development of endocrine resistance was a major obstacle to existing treatments. Novel approaches showed that the expression of ER was at least partially dependent on the regulation of CAF-derived EVs. It was reported by Shah *et al.* that miR221/222 in the exosomes at least partially lead to MAPK-related ER repression in the basal-like BC subtype[132]. miR-221 shuttled by stromal microvesicles could transfer into tumor cells by endocytosis and remarkably triggered the ER^{lo}/Notch^{hi} feed-forward loop, which converts noncancer stem cells into CSCs, thus contributing to endocrine resistance in patients with luminal BC[133]. A novel CAF subpopulation, CD63$^+$ CAFs, can release large amounts of miR-22 encapsulated by EVs, which directly target ERα and PTEN after being taken up by BC cells. The loss of ERα and PTEN expression subsequently led to decreased tamoxifen sensitivity in BC patients[134]. In ER$^+$ BC, the transition from a hormonal therapy-sensitive state to a treatment-resistant state was found to be tightly associated with host mtDNA-mediated oxidative phosphorylation (OXPHOS). Sansone *et al.* proposed that CAF-derived EVs play an essential role in the horizontal transfer of the full mitochondrial genome into BC cells, which substantially induces cancer stem-like cells, thus contributing to endocrine therapy resistance in BC patients[135].

THE ROLE OF IMMUNE CELLS IN EV-BASED CROSSTALK IN BC MICROENVIRONMENT

The immune cell population comprises functionally diverse subtypes, such as T cells, B cells, and natural killer (NK) cells, which are essential for protective immunity against pathogens and malignancies[136,137].

Cancer cell-derived EVs deliver bioactive molecules to immune cells to establish an immune escaping and immunosuppressive microenvironment. Exosomes derived from malignant cells decrease the expression of NKG2D on NK cells and CD8$^+$ T cells, resulting in a reduction in their cytotoxic capabilities *in vitro*, thereby facilitating immune evasion and tumor progression[138]. In BC, an increase in PD-L1-shuttled EVs secreted from BC cells following oscillatory strain leads to additive T cell suppressive functions in the TME[139]. Similarly, it has been reported that a TGF-β type II receptor (TβRII) encapsuled by BC-derived EVs can trigger CD8$^+$ T cells to enter an exhausted state, thus leading to the failure of immunotherapy[140].

CAF-derived EVs can also induce immune tolerance and facilitate immune evasion by modulating the activity and functionality of immune cells[141]. In pancreatic ductal adenocarcinoma, CAF-derived EVs carrying lncRNA RP11-161H23.5 have been shown to induce immune escape by downregulating HLA-A expression levels and inhibiting the activation of CD8$^+$ T cells[142]. Additionally, Shang *et al.* discovered that hypoxia-induced CAF-derived exosomes encapsulating circHIF1A promoted the proliferation and invasive activity of hepatocellular carcinoma while inhibiting the cytotoxicity of CD8$^+$ T cells through the upregulation of PD-L1 expression[143]. Although increasing evidence has proven the immunoregulatory

function of CAFs in BC, few studies have focused on the role of EVs in this process. According to Liao *et al.*, suppression of FAP^+ CAFs significantly contributes to their polarization from Th2 to Th1 cells in the TME, which attenuates tumor angiogenesis and lymphangiogenesis[144]. Moreover, CAFs in BC enhance the infiltration and differentiation of $CD4^+CD25^+$ Tregs via CXCL12/SDF1-α, thereby hindering the function of effector T cells[145]. Recently, integrated transcriptomics and proteomics analyses revealed an EV-specific signaling network to predict the immunosuppressive effects of CAF-released EVs on macrophages and $CD8^+$ T cells[146]. However, the underlying mechanism remains to be elucidated.

DISCUSSION

In recent years, the incidence of cancer has increased, and cancer is the leading cause of mortality worldwide. BC is the most prevalent malignant tumor among women and represents a significant threat to women's lives and health[147]. Although personalized comprehensive treatment approaches have significantly increased the survival rates of patients, tumor recurrence and metastasis are still the core problems affecting the outcomes of patients with malignancies[148]. In recent years, advances in technologies have allowed a deeper understanding of the TME. This comprehensive network of cellular organization, which consists of multiple cell types, was shown to play a dual role[62,149]. Along with the development and progression of cancer, numerous factors within the TME can not only exert antitumor effects by damaging immunogenic tumor variants but also fuel the aggressiveness of malignant cells by shaping tumor immunogenicity[62].

CAFs can promote tumor growth by providing cancer cells with a more proliferative and invasive nature[150]. To the best of our knowledge, there are multiple methods of intercellular communication between CAFs and BC cells, among which the secretory properties of CAFs play essential roles in the reconstruction of the TME. For example, fibroblast growth factors (FGFs) expressed in stromal fibroblasts effectively trigger the paracrine stimulation of cancer cells by activating fibroblast growth factor receptors (FGFRs), which leads to tumor progression[151]. It has been reported that CAF-derived basic fibroblast growth factor (bFGF/FGF2) can substantially lead to BC proliferation via sharply increasing the phosphorylation of Akt[152]. Furthermore, the activation of FGFR3, which is expressed on BC cells, contributes to resistance to endocrine therapy through the MAPK/PI3K signaling pathway[153]. Recently, emerging evidence has demonstrated that EVs are also deeply involved in the communication between CAFs and cancer cells in a variety of pathophysiological conditions.

EVs are heterogeneous lipid bilayer vesicles released by living cells that are associated with various biological processes as intermediaries for cell-cell interactions[154]. In addition to approaches in cancer immunology, increasing evidence has indicated that EVs play indispensable roles in the modulation of the immune response in the TME[31]. As depicted in Figure 1, bioactive molecules contained in BC-derived EVs effectively lead to differentiation from NFs to CAFs, while various types of CAFs could, in turn, regulate the behavior of BC cells in an EV-dependent manner.

Scientists found that the diffusion and capture of EVs are modulated in a more controlled way than they expected[155]. However, the regulatory mechanism of EV generation is yet to be elucidated. Hypoxia is a crucial hallmark of various malignancies. On the basis of the neoplastic immune context, hypoxia-mediated processes elicit complicated intercellular contacts, and recent studies revealed that EVs might play a pivotal role in such processes[156]. It has been reported that the resistance-associated lncRNA H19 is markedly overexpressed in EVs derived from hypoxia-induced CAFs[128]. Hypoxia-induced activation of the oxidized ataxia-telangiectasia mutated (ATM) gene can phosphorylate both BNIP3 and ATP6V1G1 to increase the number of EVs secreted from breast CAFs by promoting the accumulation and fusion of autophagosomes[99]. In addition, reactive oxygen species (ROS)-induced autophagy has been shown to be

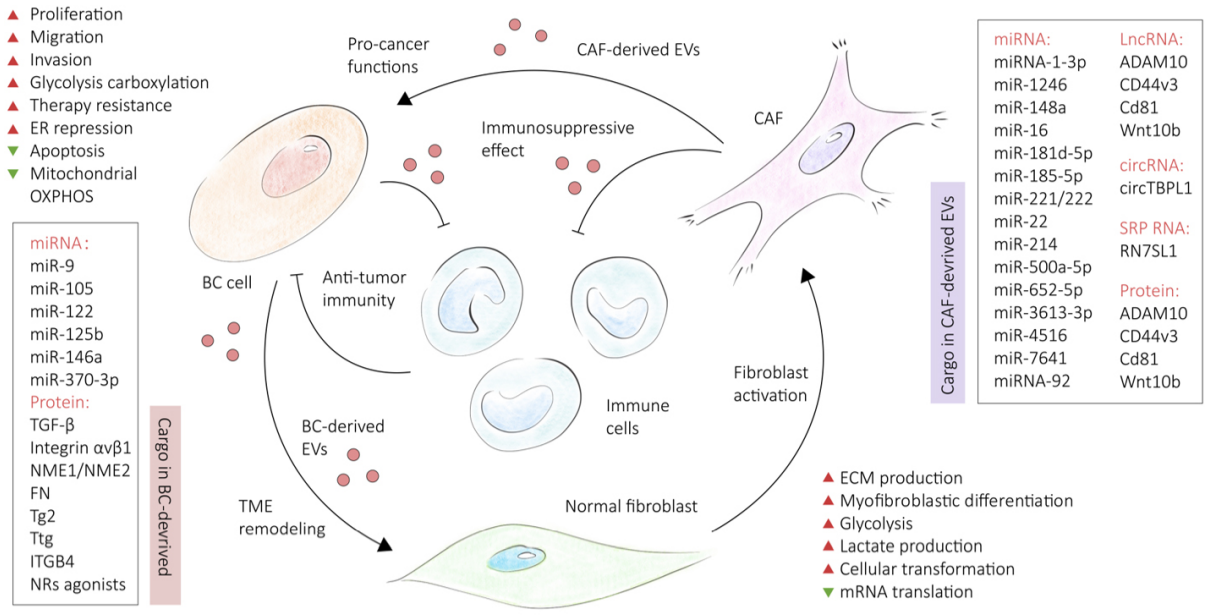

Figure 1. Intercellular crosstalk between EVs in the TME.

responsible for the loss of CAV-1 and subsequently triggers the HIF-1α signaling pathway under ROS-mediated pseudohypoxic conditions[157]. In BC, genotoxic chemotherapy-induced production of ROS in CAFs could lead to TCF12-dependent diffusion of EVs, thus facilitating chemoresistance in tumor cells[126].

Focal adhesion kinase (FAK) is a cytoplasmic protein tyrosine kinase upregulated in numerous advanced-stage solid tumors, which modulates adhesion-related cell migration, proliferation, and drug resistance[105]. In a model of hypertrophic scar formation, fibroblast-specific FAK-deficient mice have enormously suppressed inflammatory response and fibrosis than animals in the control group[158]. a recent study revealed that the activation of FAK in CAFs plays a central role in mediating cell-cell interactions with BC cells via the regulation of secreted EVs[105]. Depletion of FAK in CAFs effectively resulted in a reduction in the protein and RNA components of these vesicles.

Notch signaling is an evolutionarily conserved pathway that directly links cell components at the cytoplasmic membrane with the modulation of transcription[15]. Fibroblasts within the TME can be directly stimulated through contact with tumor cells via the activation of Notch signaling[159]. Typically triggered by BC, upregulation of the stromal NOTCH-MYC pathway in CAFs is also tightly associated with alterations in the composition of EVs. The activation of the signaling pathway resulted in increased POL3-dependent expression of the exosomal srpRNA RN7SL1. Unshielded RN7SL1 taken up by recipient neoplastic cells could, in turn, promote tumor progression and drug resistance in BC patients[116].

Increasing evidence has demonstrated the ability of nonmalignant stromal components to normalize tumor cells, indicating the promising role of strategies targeting protumoral communication between cancer cells and fibroblasts in the immunosuppressive TME[160]. In BC, a CAF regulator named dasatinib was shown to have synergistic antitumor effects with an immunogenic cell death (ICD) inducer (epirubicin) by reprogramming CAFs through the modulation of apoptotic vesicles[96]. In addition, scientists have reported that integrin αvβ1 plays a key role in the retention of EVs; thus, suppressing the integrin αvβ1 complex with a galectin-3 inhibitor could significantly attenuate the differentiation of fibroblasts into CAFs[161]. According

to Papi *et al.*, nuclear receptors such as pioglitazone can also abrogate the functions of hypoxic MCF7-derived exosomes, thereby promoting a proinflammatory phenotype of fibroblasts in the BC stem cell niche[65].

In addition, tumor-derived exosomes are released by tumor cells and carry substances that can reflect the features of parental tumor cells. Therefore, exosomes can be used as tumor diagnostic markers. A promising clinical trial (NCT03974204) is ongoing to explore the use of exosomes in cerebrospinal fluid as diagnostic markers in BC patients with leptomeningeal metastasis[162]. Although multiple types of EVs, such as exosomes and microvesicles, play pivotal roles in the TME, only exosomes have a suitable size for potential application as novel drug vehicles in cancer treatment[163]. After artificial modification, engineered exosomes carrying antitumor agents could efficiently release these cargos into tumor sites with fewer side effects[164]. Recently, Li *et al.* reported a HER2-specific exosome-T vaccine that could substantially augment immune functions in patients with HER2-positive BC[165].

CONCLUSION

Tumor development is a comprehensive process that is not only interrelated with biological alterations inside tumor cells, such as altered cell behavior and dysregulated metabolic pathways, but also related to interactions with surrounding stromal cells. EVs are among the most significant media involved in cell-cell contacts. Hence, EV-dependent communication between breast tumor cells and CAFs has received much attention in recent decades. Here, we systematically reviewed the intercellular networks associated with EV transportation and the underlying mechanisms of the phenotypical alterations in both fibroblasts and malignant cells. Strategies targeting secreted EVs in the TME are likely to play a pivotal role in the treatment of patients with BC.

DECLARATIONS

Authors' contributions

Made substantial contributions to the conception and design of the study, supervision: Yang Q
Writing - original draft preparation: Li C, Yang C
Writing - review and editing, funding acquisition: Yang Q, Li C

Availability of data and materials

Not applicable.

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Conflicts of interest

All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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