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Extracellular vesicle-orchestrated crosstalk between cancer-associated fibroblasts and tumors

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ABSTRACT

Communication networks in the tumor microenvironment (TME) play a crucial role in tumor progression. Cancer-associated fibroblasts (CAFs) are among the most abundant stromal cells in the TME. Bidirectional signal transduction between cancer cells and CAFs within the TME is important for cancer development and treatment responsiveness. Extracellular vesicles (EVs) carrying proteins, miRNAs, and other biomolecules are secreted into the extracellular matrix (ECM), which has been demonstrated to be an important communication medium between tumors and CAFs. Tumors regulate the activation of CAFs by secreting EVs. Conversely, CAFs can also affect tumor proliferation, metastasis, and therapeutic resistance through EVs. Here, we will classify EV cargoes and discuss the role of EV-mediated interactions between CAFs and tumors, reviewing current knowledge in combination with our confirmed results.

Introduction

Tumor progression is closely related to the tumor microenvironment (TME). Endothelial cells, fibroblasts, immune cells, and other non-tumor cells exist in the TME [1]. Cytokines, growth factors, hormones, extracellular matrix (ECM), and other extracellular components are also important components of the microenvironment [1]. Tumors recruit stromal cells by secreting growth-stimulating agents and intermediate metabolites to reshape the tissue structure [2]. Conversely, stromal cells also regulate tumor growth, invasion, metastasis, and therapeutic resistance by secreting cytokines [3]. Communication networks in TME play a crucial role in tumor progression.

Cancer-associated fibroblasts (CAFs) are one of the most abundant stromal cells in the TME and are derived from the pathological activation of persistent fibroblasts, mesenchymal stem cells, and adipocytes in the microenvironment matrix [4]. CAFs promote tumor migration and invasion by reconstructing ECM and participating in proteolysis, cross-linking, and assembly of the ECM [5]. In addition, tumors can promote stromal cell activation into the CAF phenotype [6]. The interaction between tumors and CAFs has a profound influence on tumorigenesis and the microenvironment components.

Extracellular vesicles (EVs), which carry proteins, miRNAs, and

Abbreviations: CAF, cancer-associated fibroblast; CCAL, colorectal cancer-associated lncRNA; CM, conditioned medium; CRC, colorectal cancer; CSCC, cervical squamous cell carcinoma; CSD, CAV1 scaffolding domain; CTGF, connective tissue growth factor; CYR61, cysteine-rich angiogenesis inducer 61; ECM, extracellular matrix; EMT, epithelial-mesenchymal transition; ER, estrogen receptor; EV, extracellular vesicle; EZH2, enhancer of zeste homolog 2; FAP, fibroblast activating protein; FGF5, fibroblast growth factor 5; FN, fibronectin; GAS6, growth retardant specific protein 6; CAV1, caveolin 1; GDF15, growth differentiation factor 15; HCC, hepatocellular carcinoma; HGF, hepatocyte growth factor; HL, Hodgkin's lymphoma; HNSCC, head and neck squamous cell carcinoma; HPLF, human periodontal ligament fibroblast; HUVEC, human umbilical vein endothelial cell; ILV, intracavinal vesicle; JAK, Janus kinase; LIF, leukemia inhibitory factor; lncRNA, long non-coding RNA; MCC, Merkel cell carcinogenic; MSC, mesenchymal stem cell; MVB, multivesicular body; ncRNA, non-coding RNA; NGF, nerve growth factor; NID1, Nidogen 1; OSCC, oral squamous cell carcinoma; PAF, paracancerous fibroblast; PDGFRS, platelet-derived growth factor receptor; PRSC, prostatic stromal cell; SACC, salivary adenoid cystic carcinoma; SNARE, soluble NSF-attachment protein receptor; SRF, serum response factor; TME, tumor microenvironment; TNBC, triple-negative breast cancer; TNFR1, tumor necrosis factor receptor 1; TP53InP1, TP53-induced nucleoprotein 1; Treg, cell regulatory T cell; tTG, tissue transglutaminase; VASH1, vasohibin 1; VEGF, vascular endothelial growth factor; YAP1, YES-associated protein 1; α-SMA, α-smooth muscle actin.

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other biomolecules, are secreted into the ECM, to be taken up by recipient cells to perform physiological functions [7]. A growing body of evidence has shown that EVs are an important communication medium between tumors and CAFs [8]. In this review, we focus on the role of EVs in the TME by reviewing current knowledge in combination with the results that we have confirmed, and discuss the role of EV-mediated interactions between tumors and CAFs (Fig. 1).

Extracellular vesicles (EVs)

EVs are typically cup-shaped, negative-staining, and round-shaped under transmission and cryogenic electron microscopy [9]. According to size and biogenic process, EVs can be divided into three main subgroups: (i) exosomes (30–100 nm), (ii) microvesicles (20–1000 nm), and (iii) apoptotic bodies (50–5000 nm) [10]. We will focus on the roles of exosomes and microvesicles in intercellular communication in the TME in this review. Exosome biogenesis begins with the budding of the membrane of multivesicular bodies (MVBs) to form intracellular vesicles (ILVs) [11]. The MVBs are then transported to the plasma membrane of the cell, where they fuse with the plasma membrane to release the exosomes [11]. The formation of microvesicles is initiated from the outward budding and plasma membrane fission, subsequently, vesicles are released into the extracellular space [12]. EVs carry a variety of signaling molecules, which are important mediators of cell-to-cell communication and play important roles in many physiological and pathological processes, including stem cell maintenance, tissue repair, immune regulation, and tumor growth.

EVs originating from different cells contain diverse contents that exert different functions. For example, EVs secreted by metastatic melanoma cells spontaneously metastasize to the lung and brain, activating pro-inflammatory signals in lung fibroblasts and astrocytes, suggesting that EV-mediated stromal cell reprogramming is a general mechanism for regulating metastatic sites in multiple distal organs [13]. In contrast, EVs derived from immune cells inherit the antitumor activity of parent cells to some extent. Activated CD8+ *T* cells from healthy mice instantaneously release cytotoxic EVs and significantly reduce tumor invasion and metastasis by reducing stromal cell apoptosis [14]. In addition, EVs derived from body fluids are of great interest to researchers; plasma-derived EVs from *Plasmodium vivax* infected patients are preferentially absorbed by human splenic fibroblasts *in vitro*; this uptake induces specific upregulation of ICAM-1 and is associated with nuclear transport of NF-κB [15]. Although EVs show great potential in the regulation of physiological and pathological functions, the current exploration of EV-mediated communication between cells is still limited to the basic mechanisms. Owing to the instability of EVs themselves and their low efficiency in physiological function regulation, EVs are still very rare in clinical translational applications. These problems are also a bottleneck that researchers need to overcome at present.

Cancer-associated fibroblasts (CAFs)

CAFs are the key components of the TME. However, due to the lack of specific markers for fibroblasts, there are inherent difficulties in determining their biological origin [16]. The simplest view from biopsy analysis at this stage is that cells with elongated epithelial, endothelial, and leukocyte markers that lack the mutations found in cancer cells may be considered as CAFs [16]. At present, the most common positive molecular markers in experiments are α-smooth muscle actin (α-SMA), fibroblast activating protein (FAP), podoplanin, vimentin, and platelet-derived growth factor receptor (PDGFRS). The negative characteristics were CD31 and cytokeratin [17].

As the name suggests, CAFs are defined by their association with cancer cells within the TME [17]. According to the existing literature, the occurrence and development of CAFs can be simply summarized as follows: fibroblasts are activated in the initial stage of tumorigenesis to produce CAFs, and then reshape the TME to induce tissue repair, thus possibly playing an anti-tumor function [17]. However, as tumors grow, this repair process may, in turn, promote tumor growth, as cancer cells use growth factors secreted by CAFs to promote their own survival and proliferation [17]. Therefore, in order to better understand the markers of CAFs, the activation of related signaling pathways, and their role in tumor progression and treatment, it is crucial to further explore the origin of CAFs.

CAFs activation

The exact sources of CAFs are not entirely clear and may be mixed. CAFs can be derived from TME cells (*e.g.*, fibroblasts, epithelial cells, endothelial cells, pericytes, and adipocytes) and distal cells (*e.g.*, bone marrow-derived mesenchymal stem cells)[17, 18]. Because of the

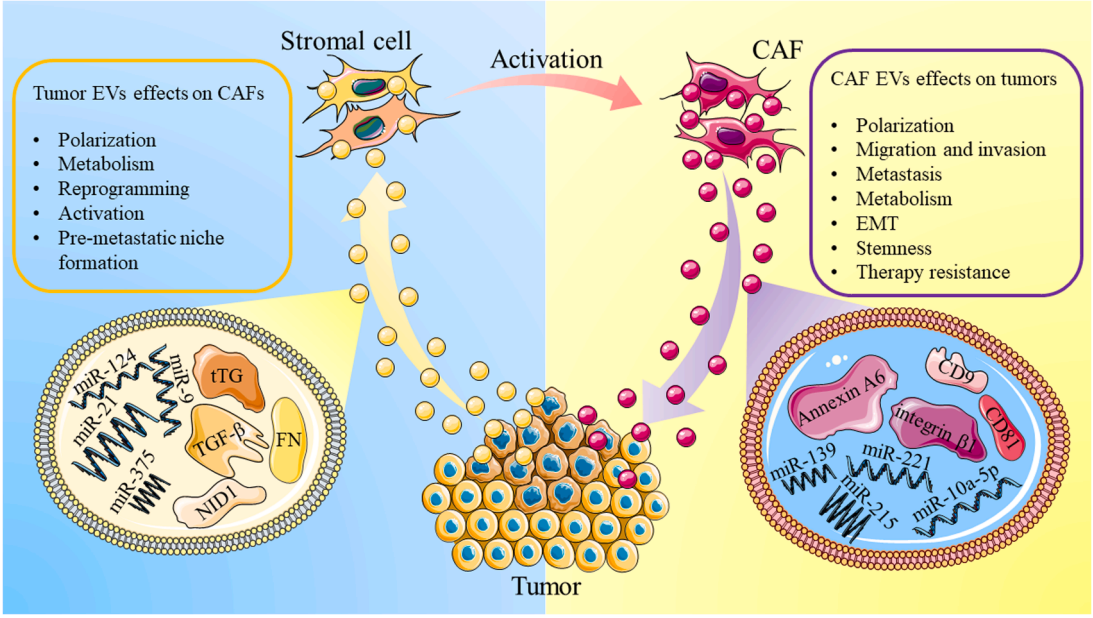

Fig. 1. EV-mediated communication between CAFs and tumors.

considerable heterogeneity of the origin of CAFs, the mechanisms of activation of different CAFs are highly varied.

Fibroblast activation signals include TGF-β family ligands and lipid-mediated lysophosphatidic acids, which promote the activity of Smad transcription factor and serum response factor (SRF), respectively; these polymerize to drive the expression of the activated fibroblast marker αSMA and increase the activity of the cytoskeleton contraction [17]. In addition, various inflammatory modulators can also promote the activation of CAFs, among which IL-1 acts through NF-κB [19]. IL-6 mainly acts on signal transduction and transcriptional activator STAT (signal transducer and transcriptional activator STAT) transcription factors [20]. Activation of CAFs is further enhanced by changes in the contractile cytoskeleton and histone acetylation, involving crosstalk and positive feedback of the Janus kinase (JAK)-STAT signal. CAFs can also be activated by physical changes in the ECM [21]. Overproliferation of transformed epithelial cells may lead to fibroblast stretch, which can activate Srf-driven transcription and YES-associated protein 1 (YAP1)--TEAD-driven transcription [17]. These transcription factors cooperatively drive the expression of a variety of CAF-related genes, including the genes encoding connective tissue growth factor (CTGF; also known as CCN2) and cysteine-rich angiogenesis inducer 61 (CYR61; also known as CCN1) [22]. In addition, stromal cell molecules, such as CTGF and CYR61, and the contractile cytoskeleton cooperate to increase tissue hardness, further driving SRF- and YAP1-dependent transcriptional programs, thus forming a self-sustaining positive feedback loop for CAFs [16]. Signals from other cells in the TME may also influence CAF activation, in addition to tumor cells. Furthermore, routine chemoradiotherapy can promote the production of CAFs and regulate their function [23]. These results suggest that CAFs have the potential to be effective targets for the clinical treatment of cancer.

CAFs function

The best-known function of CAFs is deposition and remodeling of the ECM in the TME [16]. This process is mainly achieved through Rho and Rab GTPase, which regulate integrin-mediated adhesion and actomyosin cytoskeleton, and is associated with downregulation of the transmembrane receptor CD36 (also known as platelet glycoprotein 4) [16]. In addition, CAFs also produce stromal cross-linking enzymes and combine with force to mediate ECM remodeling, which contributes to increasing the hardness of tumor tissues [24]. The remodeling of ECM by CAFs can not only promote the local invasion of tumors, but also provide the necessary survival conditions for distal metastasis [24]. Reactivation of CAFs in secondary sites produces stromal components (*e.g.*, tenascin and periostin) through a variety of mechanisms that provide support signals for metastatic cancer cells [25]. The increase in tissue hardness mediated by CAFs triggers pro-survival and proliferation signals in cancer cells [26]; combined with increased mechanical stress, blood vessels collapse, leading to local hypoxia, which promotes a more aggressive cancer phenotype [27].

CAFs are also important sources of growth factors, cytokines, and soluble factors that promote tumor growth and regulate therapeutic responses [28]. The production of TGF-β, leukemia inhibitory factor (LIF), growth retardant specific protein 6 (GAS6), fibroblast growth factor 5 (FGF5), growth differentiation factor 15 (GDF15), and hepatocyte growth factor (HGF) promote the invasion and proliferation of cancer cells [29]. In contrast, CAF secretion also affects other components of the TME. In hepatocellular carcinoma, CAFs have been reported to promote angiogenesis through vascular endothelial growth factor (VEGF) secretion, which is related to the upregulation of the enhancer of zeste homolog 2 (EZH2) and further inhibition of vasohibin 1 (VASH1) [30].

Furthermore, many cytokines and chemokines are produced by CAFs, which act on a range of immune cells, leading to immunosuppressive and pro-immune outcomes [31]. Tumor cells are first destroyed by immune cells; then, tumor cells and immune cells coexist; finally, tumor cell subcloning changes its immunogenicity, evades immune recognition, and promotes tumor progression [32]. In this case, CAFs modulate tumor immune responses to promote tumor progression, including interactions with a variety of immune cells, such as CD8+*T* cells, regulatory T (Treg) cells, macrophages, and dendritic cells [32]. Xu et al. performed transcriptome RNA sequencing and reverse transcriptome quantitative polymerase chain reaction analysis on human periodontal ligament fibroblasts (HPLFs) that had ingested salivary adenoid cystic carcinoma cell-derived EVs, and the results confirmed that HPLFs were cultured as a pre-tumorigenetic phenotype [33]. This phenomenon is associated with EV-mediated stimulation of proinflammatory cytokines and secretion of nerve growth factor (NGF) [33]. In addition, secretion analysis of EVs collected from Hodgkin's lymphoma (HL) cells revealed enhanced release of pro-inflammatory cytokines (such as IL-1α, IL-6, and TNF-α), growth factors (G-CSF and GM-CSF), and pro-angiogenic factors (such as VEGF) [34]. CAFs form a network with a variety of immune cells in the TME through related cytokines, making the mechanism of their regulation of immunity and inflammation extremely complex, which still needs to be further explored.

As an important medium of information communication between cells, direct interaction between EVs and cancer cells has been extensively discussed in the literature. Previous studies have shown that tumor cell-derived EVs can regulate the activation of CAFs [35]. Conversely, CAFs can also affect tumor progression, metastasis, and treatment by secreting EVs [36]. This review summarizes the roles of different components carried by EVs in the interaction between CAFs and tumor cells.

Role of tumor-derived EV contents on CAFs

Tumor-derived EVs play an important role in the formation of local microenvironments, including fibrosis, angiogenesis, escape from immune surveillance, and even metastasis. Interestingly, EVs derived from the body fluids of tumor patients have been shown to promote the proliferation of normal fibroblasts [37]. As the main component of the TME, signal communication between fibroblasts and tumor cells plays an important role in the occurrence and development of tumors. Goulet et al. demonstrated that healthy primary bladder fibroblasts treated with EVs of bladder cancer showed high expression of α-SMA and FAP as CAFs [38]. In addition, the phenomenon in which tumor-derived EVs promote the activation of CAFs may be related to the aggressiveness of tumors [39], and the physical characteristics of the TME (such as the hardness of surrounding stroma) [40]. On the other hand, CAFs from different sources have different responses to EVs secreted by tumors. For example, the number of CAFs differentiated from human umbilical vein endothelial cells (HUVECs) increases with melanoma-derived EVs, showing significant morphological and molecular changes and marked moveability [41]. Mesenchymal stem cell (MSC)-derived EVs inhibit colorectal to mesenchymal transition, induce angiogenesis and maintain endovascular homeostasis [41]. EVs carry different biomolecules to perform different physiological functions in recipient cells. We will classify the current common EV carriers and elaborate on the effects of different components carried by tumor-derived EVs on CAFs.

Protein

As previously mentioned, the TGF-β family of ligands is a major signaling molecule for the activation of CAFs. Tumor-derived EVs promote the activation of CAFs by carrying TGF-β-related proteins [42]. TGF-β was found to be expressed on the surface of EVs and related to the transmembrane proteoglycan β-glycan, which plays a role in stimulating Smad-dependent signaling [42]. On the other hand, Gu et al. confirmed that gastric cancer cells trigger the differentiation of human umbilical cord-derived MSCs to CAFs through TGF-β transfer mediated by EVs and activation of the TGF-β/Smad pathway [43]. This phenomenon also

illustrates the diversity of CAFs from another perspective. In addition, Antonyak et al. found that EVs secreted in two types of cancer cells impart transformational characteristics to normal fibroblasts and epithelial cancer cells, which require the transporter cross-linking enzyme tissue transglutaminase (tTG) to cooperate with the substrate fibronectin (FN) [44]. Furthermore, FN levels in the ECM have been shown to be involved in the dynamic relationship between tumors and stromal cells in the TME [45]. The results enrich the CAF activation mechanism and provide new ideas for CAFs as tumor therapeutic targets.

In addition to regulating the local TME, tumor-derived EVs can also provide a growth-friendly supporting environment for tumor metastasis by promoting the activation of CAFs in distal tissues. Circulating EVs isolated from the plasma of patients with metastatic prostate cancer induced reprogramming of normal human prostate fibroblasts to express high levels of α-SMA, IL6, and MMP9 [46]. This process is mediated by MYC and AKT1 kinases in the stroma, which strongly promotes the establishment of a tumor-supporting environment [46]. The lungs are often considered the first port of call for cancer metastasis. For example, Nidogen 1 (NID1) in EVs derived from metastatic liver cancer cells activates fibroblasts, which secrete tumor necrosis factor receptor 1 (TNFR1), promote lung colonization of tumor cells, and enhance the growth and viability of hepatocellular carcinoma (HCC) cells [47]. Human lung fibroblasts showed more aggressiveness when stimulated by osteosarcoma cell-derived EVs, which was closely related to the presence of TGF-β1 in osteosarcoma cell-derived EVs [48].

Changes in the environment affect the EV cargo, which in turn affects their physiological function [49]. Ramteke et al. analyzed the role of EVs from hypoxic prostate cancer cells in promoting the CAF phenotype in prostatic stromal cells (PRSC) [50]. The expression of multiple PRSC signaling molecules (TGF-β2, TNF1α, IL6, TSG101, Akt, ILK1, and β-catenin) was increased after treatment with EVs [50]. Combined with the characteristics of hypoxia in the TME, the synergistic interaction between the tumor and stromal cells in the microenvironment may be more obvious. Interestingly, we have shown that tumor cells can secrete TGF-β in an EV-independent manner and that hypoxia promotes this process [6]. Hence, tumor cells secrete TGF-β and EVs to mediate CAF-like differentiation of fibroblasts. This conclusion provides a new perspective for exploring the mechanism of CAF activation, while also providing a new idea for the participation of EVs in information communication between tumor and stromal cells.

In addition, the growth cycle of tumor cells also affects the regulation of CAF function. Fibroblasts activated by EVs in early colorectal cancer have high proliferative and angiogenic abilities, and show increased expression of angiogenic (IL8, RAB10, NDRG1) and proliferative (SA1008, FFPS) proteins [51]. In contrast, fibroblasts activated by advanced cancer EVs have been demonstrated to have a surprising ability to invade through the ECM by upregulating the pre-invasion regulator of membrane protrusion (PDLIM1, MYO1B) and enhancing the secretion of matrix remodeling proteins (MMP11, Emmprin, ADAM10) [51]. EVs of primary and metastatic tumors produce phenotypically and functionally different subsets of CAFs, which may play different roles in tumor progression. Interestingly, ITGB4 overexpressing triple-negative breast cancer (TNBC) cells provide ITGB4 protein to CAFs via EVs, thereby inducing BNIP3L-dependent mitochondrial phagocytosis and lactic acid production in CAFs [52]. Correspondingly, the overexpression of ITGB4 in CAF medium promoted the proliferation, epithelial cell-to-mesenchymal transformation, and invasion of breast cancer cells [52]. ITGB4-induced mitochondrial autophagy could be used as potential targeted therapy for cancer.

MiRNA

In addition to proteins, miRNAs play an important role in the EV-mediated activation of CAFs in tumors (Table 1). Zhou et al. confirmed that EVs secreted by melanoma cells can induce the reprogramming of fibroblasts into CAFs [53]. Although tumor angiogenesis is regulated by a variety of factors, EV delivery of miR-155 may be a potential target for the control of melanoma angiogenesis and could be used to develop new strategies for the treatment of melanoma [53]. Besides, several miRNAs have also been shown to activate CAFs through EVs in different cancers, such as miR-1423p in lung cancer [54] and miR-124 in ovarian cancer [55]. We will elucidate the regulatory role of EVs derived from different tumors on CAFs.

Table 1
Effects of miRNA carried by extracellular vesicles derived from tumors on cancer-associated fibroblasts.

Type of cancer	miRNA	Main effects	Ref.
Breast cancer	miR-9	Triple-negative breast cancer-secreted miR-9 can be transferred via extracellular vesicles to recipient normal fibroblasts and this uptake results in enhanced cell motility.	[58]
	miR-125b	MiR-125b is transferred through extracellular vesicles from breast cancer cells to normal fibroblasts within the tumor microenvironment and contributes to their development into cancer-associated fibroblasts.	[56]
	miR-146a	Breast cancer-derived extracellular vesicles regulate cell invasion and metastasis in breast cancer via miR-146a to activate cancer associated fibroblasts.	[57]
	miR-21	Hepatocellular carcinoma-derived extracellular vesicle miRNA-21 contributes to tumor progression by converting hepatocyte stellate cells to cancer-associated fibroblasts.	[61]
Liver cancer	miR-1247–3p	High-metastatic hepatocellular carcinoma cells secrete extracellular vesicle miR-1247–3p that directly targets B4GALT3, leading to activation of β1-integrin–NF-κB signaling in fibroblasts.	[64]
Lung cancer	miR-142–3p	Extracellular vesicles associated miR-142–3p promote the cancer-associated fibroblast phenotype in lung fibroblast cells which is independent of TGFβ signaling.	[54]
Ovarian cancer	miR-124	Extracellular vesicle transfer of miR-124 inhibits normal fibroblasts to cancer-associated fibroblasts transition by targeting sphingosine kinase 1 in ovarian cancer.	[55]
Skin cancer	miR-375	Merkel cell carcinoma-derived extracellular vesicle-shuttle miR-375 induces fibroblast polarization by inhibition of RBPJ and p53.	[100]

Breast cancer

Vu et al. demonstrated that mir-125b was transferred from breast cancer cells to normal fibroblasts in the tumor microenvironment by EVs and promoted their development into cancer-associated fibroblasts in a mouse triple negative breast cancer model [56]. In addition, Breast-cancer-derived EVs promote the activation of CAFs through the miR-146a/TXNIP axis, which activates the Wnt pathway, thereby enhancing the invasion and metastasis of tumor cells [57]. MiR-9 has also been shown to have similar functions in breast cancer models [58]. In conclusion, using these small molecules as targets to cut off tumor metastasis can provide a new direction for the prevention and treatment of cancer metastasis in clinical practice.

Metabolic regulation of the TME is important for tumor development. CAF-mediated metabolic reprogramming contributes to the sustained growth of tumors by regulating the shared metabolic environment. Yan et al. demonstrated a mechanism model involving EV-encapsulated miR-105 secreted by breast cancer, in which miR-105 is induced by the oncoprotein Myc in cancer cells, which in turn activates Myc signaling in CAFs to induce metabolic programming [59]. Interestingly, when nutritionally adequate, miR-105-reprogrammed CAFs enhance glucose and glutamine metabolism, thereby providing fuel for neighboring cancer cells [59]. When nutrients are scarce and metabolic

by-products accumulate, CAFs are detoxified by converting metabolic waste (including lactic acid and ammonium) into energy-rich metabolites [59]. The different metabolic characteristics of miR-105-mediated CAFs during changes in the metabolic environment have led to a new understanding of the physiological functions of CAFs.

Digestive system tumor

MiRNAs analysis of EVs from gastric cancer revealed that several miRNAs play a role in the induction of fibroblast chemokines such as CXCL1 and CXCL8 [60]. Moreover, abnormal activation of CXCL1 and CXCL8 in clinical CAFs is associated with poor survival in patients with gastric cancer, and this association may provide a new target for anticancer therapy [60]. In addition to fibroblasts, tumor-derived EVs can also activate other cell types to transform into CAFs by the delivery of miRNAs. EVs of hepatocellular carcinoma carry miRNA-21 to transform hepatocellular stellate cells into cancer-associated fibroblasts and promote tumor progression [61].

A variety of miRNAs have been shown to regulate the expression of TP53, one of the most studied tumor suppressor genes, thus playing a role in tumor progression. Yoshii et al. demonstrated from another perspective that miRNAs and TP53 play a role in fibroblast activation [62]. After fibroblasts were treated with EVs from TP53-deficient colon cancer cells *in vivo*, the CAF phenotype in fibroblasts was promoted [62]. Microarray analysis of EVs confirmed that several microRNAs (miR-1249–5p, miR-6377–5p, and miR6819–5p) were upregulated in TP53-deprived EVs [62]. These miRNAs have been shown to functionally inhibit TP53 expression in fibroblasts [62]. In addition, TP53-induced nucleoprotein 1 (TP53InP1) has also been shown to be a target of miR-155 in fibroblasts, while downregulation of TP53InP1 protein levels contributes to fibroblast activation [63]. The downregulation of TP53 enhances the chemotaxis of fibroblasts to the CAF phenotype, which can be regulated by miRNAs. The results provide a theoretical basis and a new perspective for CAFs to become clinical tumor therapeutic targets.

MiRNA also play a key role in the establishment of EV-mediated microenvironments in distal metastases. Similarly, highly metastatic HCC was more capable of converting normal lung fibroblasts to CAFs than those with low metastatic HCC, which was mediated by miR-1247–3p delivered via EVs [64]. Furthermore, clinical data have shown that high serum EV miR-1247–3p levels are associated with lung metastasis in HCC patients [64].

Head and neck cancer

Hypoxia, one of the main characteristics of the TME, plays an important role in the regulation of EVs from tumor cells. We have demonstrated that hypoxic head and neck squamous cell carcinoma (HNSCC) cells can induce CAF-like differentiation of fibroblasts by secreting TGF-β and EVs containing miR-192/215 miRNA levels [6]. The target gene of the miR-192/215 family is caveolin 1 (CAV1), which regulates CAF-like differentiation of fibroblasts by inhibiting TGF-β/Smad signaling [6]. Restoration of CAV1 levels with CAV1 scaffolding domain (CSD) peptides inhibited hypoxic EV- and TGF-β-induced CAF-like differentiation [6]. Finally, we measured miR-192 and miR-215 levels in EVs of patients with HNSCC and found that miR-192/215 expression levels in tumor tissue-derived EVs were significantly correlated with nuclear HIF-1α and αSMA expression levels [6]. Furthermore, miR-215 levels in tumor tissue-derived EVs were significantly associated with poorer overall survival in patients with HNSCC, suggesting that tumor tissue-derived EVs may contain substances that are indicative of hypoxia and aggressive TME [6]. The use of CSD peptides to restore CAV1 levels may be a potential therapeutic strategy for treating HNSCC in hypoxic microenvironments [6].

Effects of CAF-derived EV contents on tumors

As one of the major components of the TME, the role of CAFs in tumor progression has not been fully clarified. The conditioned medium (CM) of CAFs verified that CAFs promoted the invasive phenotype of non-invasive bladder cancer cells by secreting IL-6-induced epithelial-mesenchymal transition (EMT), which proved that the secretion of CAFs could play a regulatory role in tumor growth [38]. EVs play an important role in the regulation of CAFs in tumors as an important medium of information communication between cells. EVs derived from primary human CAFs have been shown to influence the proliferation, survival, migration, and invasion of oral squamous cell carcinoma (OSCC) cells [65]. Itoh et al. found that CAFs induced apoptosis in gastric cancer cells, thereby preventing the expansion and invasion of cancer cells, which ultimately promoted CAF-dominated tumor invasion [66]. Therefore, CAFs not only promote tumors, but also have certain anti-tumor effects. In addition, metabolomic analysis of EVs from CAFs revealed that they contained complete metabolites (including amino acids, lipids, and TcaCycle intermediates), which were used by cancer cells for central carbon metabolism and tumor growth under nutrient deficiency or nutrient stress conditions [67]. The results substantiate the mechanism of metabolic reprogramming of the TME by CAFs. The reason why CAFs have become one of the important targets of clinical transformation is closely related to the role they play in tumor progression, metastasis and drug resistance [68]. Next, we summarize the effects of the different components carried by CAF-derived EVs on tumors.

Protein

Tumors and CAFs are interdependent and complement each other during growth. In fact, there are many ways in which CAFs promote tumor metastasis by secreting EVs. For example, the promotion of lung fibroblast activation by CAF-derived EVs is a key event in the pre-metastatic niche. Kong et al. demonstrated that integrin α2β1 mediated the uptake of CAF-derived EVs by lung fibroblasts in transplanted tumor mice, inducing the formation of a pre-metastatic niche in mice, thereby increasing lung metastasis in salivary adenoid cystic carcinoma (SACC) [69]. The significant increase in plasma EV integrin β1 in transplanted tumor mice with lung metastasis risk suggests that plasma EV integrin β1 may be a promising biomarker for early prediction of SACC metastasis [69].

Another mechanism is that the uptake of CAF-derived EVs by tumor cells improves their migration and invasion ability, thus leading to enhanced metastasis of tumors. However, the same EV protein mediates motor ability enhancement of tumors, but the mechanism of action is not the same. The formation of the ANXA6/LRP1/TSP1 complex is limited to CAFs, so the enhanced aggressiveness of PDA is mediated by the uptake of the CAF-derived EV-carrying complex by tumor cells [70]. In addition, CD9-positive EVs from CAFs may stimulate the migration ability of scirrhous-type gastric cancer cells [71]. However, CD81-positive EVs can activate the autocrine Wnt-PCP signal to drive the invasive behavior of breast cancer cells [72]. There seems to be similarities in the end results despite different mechanisms of cancer invasion. A better understanding of the mechanism of tumor metastasis will provide a more abundant theoretical basis for clinical cancer treatment.

CAFs are currently sought-after targets for clinical cancer therapy, and their roles in regulating the therapeutic sensitivity of tumors have attracted extensive attention. CAFs promote dryness and increase radiation resistance in colorectal cancer (CRC) cells, and EVs from CAFs play a key role in this process by activating the TGF-β signaling pathway [73]. The molecular mechanism of tumor drug resistance induced by CAFs is complex. EVs of CAFs carry Annexin A6, which plays a key role in network formation and drug resistance in ECM cells by activating FAK-YAP [74]. In addition, Wnt proteins in EVs can induce dedifferentiation of cancer cells, thereby promoting chemotherapy resistance in CRC [75]. Therefore, exploring the mechanism of CAF-mediated tumor therapy resistance is the only way to improve the clinical efficacy of

tumor therapy.

Furthermore, to better understand the role of CAFs in the stroma of TME, Principe et al. performed a comprehensive proteomic analysis of the secreted factors of CAFs, including EVs, which resulted in the identification of 4247 proteins [76]. It provides a useful resource for future research on the mechanisms of CAFs and biomarker studies. However, investigations on the regulation mechanism of EV-proteins in tumor microenvironment are limited currently (Table 2), and more efforts are being devoted to further exploration.

MiRNA

miRNAs have been found to be involved in TME remodeling and tumor-stromal cell interactions [77]. EVs were purified from the co-culture system of cancer cell lines and normal fibroblasts, and their miRNA expression profiles were analyzed [78]. The results suggested that the pathways involved in cell adhesion, endocytosis, and cell junctions might be related to the CAF phenotype and tumor progression [78]. Therefore, it can be inferred that CAFs regulate tumor progression by carrying miRNAs through EVs, but their physiological function needs to be analyzed in detail. MiR-10a-5p in CAF-EVs promoted angiogenesis and tumorigenicity of cervical squamous cell carcinoma (CSCC) cells by inhibiting the activation of Hh signaling by TBX5[79]. Just as the initial impression of CAFs themselves is consistent, the EVs secreted by CAFs still have the function of tumor promotion, but the specific types of miRNAs and the mechanism of their mediation still need to be further explored.

MiRNAs derived from CAF-EVs promote tumor migration and invasion

Among the many tumor-promoting effects of CAFs, the ability of tumor migration and invasion, which represents the metastatic potential of tumors, has always been a focus of research. Wang et al. found that 13 miRNAs were significantly upregulated in EVs from CAFs and corresponding paracancerous fibroblasts (PAFs) through miRNA microarray analysis [80]. CAF-derived EVs deliver miR-1228 to promote the invasion and migration of osteosarcoma by targeting ScaI [80]. Similarly, CAFs can improve tumor migration and invasion by delivering miR-382–5p (OSCC) [81], miR-139 (gastric cancer) [82], and miR-369 (lung squamous cell carcinoma) [83]. Using these miRNAs as therapeutic targets may improve the inhibitory effect of cancer metastasis in clinical practice.

Table 2
Regulations of protein carried by extracellular vesicles derived from tumors or cancer-associated fibroblasts.

Type of cancer	Protein	Main effects	Ref.
Osteosarcoma	TGF-β1	Human lung fibroblasts showed more aggressiveness when stimulated by osteosarcoma cell-derived EVs, which was closely related to the presence of TGF-β1 in osteosarcoma cell-derived EVs.	[48]
Liver cancer	Nidogen 1	Nidogen 1 in EVs derived from metastatic liver cancer cells activates fibroblasts, which promoting lung colonization of tumor cells and enhancing the growth and viability of hepatocellular carcinoma cells.	[47]
Gastric cancer	TGF-β	Gastric cancer cells trigger the differentiation of human umbilical cord-derived MSCs to CAFs through TGF-β transfer mediated by EVs and activation of the TGF-β/Smad pathway.	[43]
	Annexin A6	EVs of CAFs carry Annexin A6, which plays a key role in network formation and drug resistance in ECM cells by activating FAK-YAP.	[74]
Head and neck cancer	integrin α2β1	Integrin α2β1 mediated the uptake of CAF-derived EVs by lung fibroblasts, inducing the formation of a pre-metastatic niche, thereby increasing lung metastasis in salivary adenoid cystic carcinoma.	[69]
Colorectal cancer	Wnt	Wnt proteins in EVs can induce dedifferentiation of colorectal cancer cells, thereby promoting chemotherapy resistance in CRC.	[75]

CAF-EV-miRNAs enhance the therapeutic resistance of tumors

Therapeutic resistance of the tumor is also one of the reasons for its popularity in therapeutic effectiveness research. Exploring the mechanism of tumor drug resistance has become an urgent obstacle for researchers and clinicians. EV-derived miR-27a produced by primary prostate fibroblasts can increase chemotherapy resistance by inhibiting P53 expression [84]. The role of CAFs in tumor drug resistance has attracted increasing attention, and they play an important role in the regulation of tumor drug resistance mediated by EVs [85]. Hormone therapy is a conventional treatment method for breast cancer, and its effects are closely related to the body's estrogen receptor (ER). Regulation of ER expression by miR-221 has been repeatedly demonstrated [86,87]. CAFs deliver miR-221 to breast cancer cells via EVs, thereby inhibiting ER expression and reducing tumor sensitivity to hormone therapy [86]. The results provide an adjuvant therapeutic target for breast cancer hormone therapy, which, in combination with gene therapy, may produce a complementary effect. The fact that the same miRNA had the same function in different tumors should have made the results even more compelling. MiR-21 has been shown to be resistant to chemotherapy mediated by CAF-derived EVs in colorectal [88] and ovarian [89] cancers. In addition, CAFs can target specific drugs or treatment modalities through EV-mediated tumor therapy resistance, making the results more accurate. For example, pancreatic cancer has gemcitabine resistance (miR-106b) [90], HNSCC cisplatin resistance (miR-196a) [91], and CRC radiation resistance (miR-93–5p) [92].

Negative tumor regulation of miRNAs derived from CAF-EVs

The above-mentioned contents are almost all the positive regulation of miRNAs carried by EVs of CAFs on the tumor-promoting effect. In fact, some miRNAs are negatively correlated with tumor progression. For example, CAF-EVs aggravate breast cancer *in vitro* and *in vivo* by decreasing miR-30e expression and upregulating CTHRC1 [93]. Li et al. revealed that CAF-mediated endometrial cancer progression is related to the loss of miR-148b in the EVs of CAFs, and promoting the metastasis of stromal cell-derived miR-148b may be a potential therapeutic approach to prevent the progression of endometrial cancer [94]. Similarly, miR-34a-5p expression was significantly reduced in CAF-derived EVs [36]. The miR34a-5p/Axl axis promotes the progression of OSCC through the Akt/GSK-3β/β-catenin signaling pathway, thereby inducing EMT to promote cancer cell metastasis [36]. In fact, these miRNAs, which are expressed at low levels in CAFs, have the potential to be biomarkers for good prognosis of cancer in clinical practice and effective targets for gene therapy. This viewpoint has been verified in animal experiments [95].

At present, there are relatively many research results on miRNAs carried by EVs from CAFs (Table 3), and the explanation of their function and the exploration of their mechanisms are relatively comprehensive. However, the overall experimental design is relatively consistent, and the conditions in the microenvironment are not completely simulated, which makes the results too ideal. For example, the tumor microenvironment is characterized by hypoxia, acidity, and inflammation. Applying these conditions to CAFs may lead to a more realistic conclusion. The treated CAFs may be closer to the body's internal environment through the pro-tumor effect mediated by EVs.

Other components

In addition to proteins and miRNAs, several EV carriers play a key

Table 3
Effects of miRNA carried by cancer-associated fibroblasts-derived extracellular vesicles on tumors.

Type of cancer	miRNA	Main effects	Ref.
Head and neck cancer	miR-382–5p miR-196a	Cancer-associated fibroblast-derived extracellular vesicle miR-382-5p promotes the migration and invasion of oral squamous cell carcinoma.	[81]
		Extracellular vesicle miR-196a derived from cancer-associated fibroblasts confers cisplatin resistance in head and neck cancer through targeting CDKN1B and ING5.	[91]
Lung cancer	miR-369	Cancer-associated fibroblast-derived extracellular vesicle microRNA-369 potentiates migration and invasion of lung squamous cell carcinoma cells via NF1-mediated MAPK signaling pathway.	[83]
Breast cancer	miR-221	Cancer-associated fibroblast-secreted extracellular vesicle microRNA221 is directly involved in ER-repression, and may contribute to the MAPK-induced ER repression in breast cancer cells.	[86]
Gastric cancer	miR-139	Extracellular vesicle miRNA-139 in cancer-associated fibroblasts inhibits gastric cancer progression by repressing MMP11 expression.	[82]
Pancreatic cancer	miR-106b	Extracellular vesicle miRNA-106b from cancer-associated fibroblast promotes gemcitabine resistance in pancreatic cancer.	[90]
Colorectal cancer	miR-93–5p	Extracellular vesicle-mediated transfer of miR-93–5p from cancer-associated fibroblasts confer radioresistance in colorectal cancer cells by downregulating FOXA1 and upregulating TGFB3.	[92]
Cervical cancer	miR-10a-5p	Extracellular vesicle-encapsulated microRNA-10a-5p shed from cancer-associated fibroblast facilitates cervical squamous cell carcinoma cell angiogenesis and tumorigenicity via Hedgehog signaling pathway.	[79]
Ovarian cancer	miR-21	Extracellular vesicle transfer of cancer-associated fibroblast-derived miR21 confers paclitaxel resistance in ovarian cancer cells through targeting APAF1.	[89]
Osteosarcoma	miR-1228	Extracellular vesicle miR-1228 from cancer-associated fibroblasts promotes cell migration and invasion of osteosarcoma by directly targeting SCAI.	[80]

role in CAF-mediated tumor progression. For example, stromal cells shed EVs containing an RNA named *RN7SL1*, which drove anti-viral signaling in recipient breast cancer cells in protein-free form, ultimately resulting in tumor growth and therapeutic resistance [96]. Besides, Herrera et al. reported for the first time that the expression of non-coding RNAs (ncRNAs) in normal mucosal tissues and EVs derived from colorectal cancer patients was analyzed by next-generation sequencing and bioinformatics [97]. Differential expression and enrichment analysis showed that the ncRNA content of EVs was significantly different from that of normal and CAFs, which may be a potential biomarker [97]. Therefore, the results contribute to the development of new non-invasive diagnostic, prognostic, and predictive methods for the clinical management of cancer patients [97]. Long non-coding RNAs (lncRNAs) have also received attention. For example, CAFs transfer lncRNA H19 via EVs, and promote dry and chemotherapy resistance in colorectal cancer [98]. Deng et al. found that lncRNA CCAL (colorectal cancer-associated lncRNA) metastases from CAFs to cancer cells via EVs, inhibiting CRC cell apoptosis *in vitro* and *in vivo*, providing oxaliplatin resistance and activating the β-catenin pathway [99]. These conclusions also remind us that the mechanism of EV delivery is not limited to proteins and miRNAs. Many biomolecules also play key roles in EV-mediated physiological regulation. We need to look beyond the usual biomolecules, and there are many more questions to explore.

Perspectives

At present, the understanding of CAFs is still relatively shallow, and many of the mechanisms involved in the activation and function of CAFs have not been elucidated. As the main component of the TME, CAFs play an irreplaceable role in tumor progression. However, the current exploration of the interaction between tumors and CAFs has not fully simulated the physiological state of the microenvironment to a certain extent. As mentioned earlier, regardless of whether the sources of EVs are tumor or stroma, the parent cells are not completely pure. When we explore the role of EVs in information communication between cells, the type or quantity of EVs may be affected by the presence of certain microenvironmental characteristics, such as hypoxia and acidity, on the parent cells. Previously, we have demonstrated that hypoxic HNSCC cells could induce CAF-like differentiation of fibroblasts through the secretion of TGF-β and EVs containing enhanced levels of miR-192/215 family miRNAs [6]. TGF-β and miR-192/215-rich EVs synergistically mediate tumor-promoting differentiation of fibroblasts [6]. Hypoxia promotes the expression of miR-215 and miR-192 through HIF-1α and NF-κB, respectively [6]. Conversely, if we apply the characteristics of the microenvironment to CAFs, it will be closer to the actual state of the microenvironment and may help explore the real mechanism of the involvement CAF-derived EVs in tumor progression.

Many clinical sample studies have shown how the amount or function of CAF correlates with outcome, so being able to target CAF would be an attractive new idea for the antitumor therapeutic family [6]. However, the wide range of CAF functions and possible interchangeability between subtypes pose challenges to the field. Therefore, patient benefits may require targeting CAF subtypes or reprogramming CAFs into normal fibroblasts or anti-tumor CAF phenotypes. In addition, EVs have been shown to play an important role in cell-to-cell communication, affecting stromal cell regulation of the TME. However, most of the evidence regarding the role of EVs in CAF involvement in tumorigenesis comes from *in vitro* and animal model studies. Therefore, it is necessary to develop new tools and research methods to apply these findings to clinical settings in order to elucidate the molecular mechanisms underlying the interaction between CAFs and cancer cells during tumorigenesis [16–18].

CRediT authorship contribution statement

Chuanshi He: Investigation, Validation, Software, Resources, Visualization, Methodology. **Linlin Wang:** Investigation, Validation. **Ling Li:** Conceptualization, Funding acquisition, Project administration. **Guiquan Zhu:** Conceptualization, Methodology, Data curation, Writing – review & editing, Funding acquisition.

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.

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