

REVIEW

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Intercellular crosstalk between cancer cells and cancer-associated fibroblasts via extracellular vesicles

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Abstract

Intercellular communication plays an important role in cancer initiation and progression through direct contact and indirect interactions, such as via secretory molecules. Cancer-associated fibroblasts (CAFs) are one of the principal components of such communication with cancer cells, modulating cancer metastasis and tumour mechanics and influencing angiogenesis, the immune system, and therapeutic resistance. Over the past few years, there has been a significant increase in research on extracellular vesicles (EVs) as regulatory agents in intercellular communication. EVs enable the transfer of functional molecules, including proteins, mRNAs and microRNAs (miRNAs), to recipient cells. Cancer cells utilize EVs to dictate the specific characteristics of CAFs within the tumour microenvironment, thereby promoting cancer progression. In response to such “education” by cancer cells, CAFs contribute to cancer progression via EVs. In this review, we summarize experimental data indicating the pivotal roles of EVs in intercellular communication between cancer cells and CAFs.

Keywords: Cancer-associated fibroblasts, Extracellular vesicles, Cancer microenvironment, Intercellular communication, Non-coding RNA, Exosomes

Background

Although cancer cells arise from genetic mutations in normal cells, the malignant phenotypes of tumours are influenced by their surrounding tumour microenvironment (TME) [1]. The TME comprises various cellular components, including fibroblasts, endothelial cells, and inflammatory cells, as well as noncellular components, such as the extracellular matrix [1]. Accumulating evidence has demonstrated that among these TME components, cancer-associated fibroblasts (CAFs) modulate tumour metastasis and tumour mechanics and influence angiogenesis, the immune system, and therapeutic

resistance [2]. Although CAFs are complex and include subtypes with protumorigenic and antitumour effects, several reports have indicated that CAFs are potential therapeutic targets for cancer treatment [2, 3]. Direct cell-to-cell contact and humoral factors such as cytokines and chemokines are considered the principal lines of communication between cancer cells and CAFs. However, recent studies have revealed that extracellular vesicles (EVs) are also regulatory players in such communication.

EVs are vesicles enclosed by a lipid bilayer membrane that include various bioactive molecules, such as proteins, mRNAs, metabolites, and microRNAs (miRNAs). Historically, EVs were initially considered “garbage bins” for exporting unnecessary intracellular components [4]. However, in 2007, Valadi et al. proposed that mRNAs packaged in EVs can be utilized for intercellular communication upon translation in recipient cells [5]. This discovery accelerated research on the role of EVs as novel

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intercellular communication tools. In particular, over the past ten years, there has been a striking expansion of EV research in cancer-related fields [6]. Various cancer-related factors packaged into EVs are transferred to recipient cells within proximal sites and distal metastatic niches. Intriguingly, Hoshino et al. indicated that integrin marks on EV surfaces could be considered a “zip-code” for delivery to specific organs [7], suggesting that cancer cells utilize EVs to confer specific features on cells in distal organs to support metastasis. In addition, cells within the TME, particularly CAFs, also regulate tumour progression, such as metastasis, by transferring EVs to cancer cells [6]. These findings imply that EVs derived from cancer cells and host-derived CAFs are involved in the formation of a suitable TME that promotes cancer progression.

In addition to the striking functions of EVs in intercellular communication, these vesicles can be detected in various body fluids, such as blood, saliva, and urine [8]. Therefore, EVs are attractive targets for improving cancer treatment and diagnosis. How do cancer cells utilize EVs to dictate the function and phenotypes of surrounding TME components to support cancer progression? This review will focus on recent advances in the interplay between cancer cells and CAFs and summarize the current knowledge regarding the functional role of EVs in the interplay between cancer cells and fibroblasts within the TME.

Nomenclature of extracellular vesicles

There are various subtypes of EVs with differential components and biogenesis processes. They are traditionally classified into exosomes, ectosomes, and apoptotic bodies based on origin and size [4, 9]. Exosomes originate from the exocytosis of multivesicular bodies (MVBs) [9, 10]. Ceramide-dependent pathways and endosomal sorting complex required for transport (ESCRT) machinery partially regulate exosome release. Exosomes can contain the following proteins: membrane transport and fusion proteins (GTPase, annexins, and flotillin), tetraspanins (CD9, CD63, and CD81), heat shock proteins (Hsc70 and Hsp90), MVB-related proteins (Alix and TSG101), lipid proteins and phospholipases. Microvesicles are generated directly from budding of the plasma membrane [11]. Microvesicles can be enriched in some lipid components and phosphatidylserine [12]. Apoptotic bodies are generated during apoptosis. Thus, they contain intracellular fragments such as organelles, membranes, and cytosolic and nuclear fragments [13, 14]. However, it is still difficult to distinguish various types of EVs because of the lack of specific protein markers for each subtype. Thus, the expert consensus in EV research encourages the use of operational names unless specific and reliable EV

markers of subcellular origin can be established [9]. (a) Physical characteristics, such as the size or density of EVs: small EVs (sEVs: <100 nm or <200 nm) and large and/or medium EVs (m/IEVs: >200 nm). (b) Biochemical composition, such as positivity of staining for CD63, CD81, and Annexin A5. (c) Description of conditions or cells of origin, such as from podocytes and apoptotic bodies. In this review, to avoid confusion, we use the term EVs for all subtypes of membrane vesicles in the extracellular space rather than specific terms such as exosomes.

What are CAFs?

To discuss the functional role of EVs in cancer-CAF interactions, we first need to define CAFs. CAFs are fibroblasts within the tumour stroma that can originate from many cell types, including resident fibroblasts, adipocytes, bone marrow-derived mesenchymal stem cells (BM-MSCs), and endothelial cells. The subtypes of CAFs include myofibroblast-like phenotypes similar to the features of activated fibroblasts during wound healing [15]. Many researchers, therefore, utilize adopted activated fibroblast markers such as alpha-smooth muscle actin (α -SMA) for the detection of CAFs [15]. However, recent promising studies and single-cell technologies have indicated that CAFs comprise diverse subtypes with distinct characteristics [16, 17]. Thus, conventional markers of CAFs are likely insufficient to detect all CAF subtypes within tumour tissue [18]. These findings are consistent with the fact that normal fibroblasts are also heterogeneous and lack unique markers that are not expressed in other cell types [2]. Although the precise definition of CAFs is still challenging, CAFs are practically considered morphologically elongated cellular components that are negative for epithelial, endothelial and leukocyte markers within tumour tissues [2]. To exclude the possibility of cancer cells undergoing epithelial–mesenchymal transition (EMT), CAFs are also defined as cells lacking genetic mutations found within the cancer cells [2].

The origin of CAFs and the signalling that mediates CAF heterogeneity remain controversial. Given the diverse subtypes in the normal fibroblast population, CAF subtypes may reflect their original tissue background. Indeed, in breast cancer, Raz et al. demonstrated that PDGFR- α -positive and PDGFR- α -negative subsets of CAFs are generated from BM-MSCs and resident fibroblasts, respectively [19]. They utilized a unique in vivo model involving BM implantation from GFP-expressing mice to MMTV-PyMT transgenic mice to track the cellular fate of BM-MSCs within the tumour mass. This study showed that BM-MSC-derived CAFs are negative for PDGFR- α expression and enhance angiogenesis and tumour growth. In contrast, in pancreatic ductal adenocarcinoma (PDAC), Tuveson's group showed that pancreatic stellate cells differentiate

into two subsets of CAFs, inflammatory CAFs (iCAFs) and myofibroblastic CAFs (myCAFs) [20]. They also showed that IL-1 signalling induces iCAFs, but TGF- β signalling antagonizes this pathway, leading to myCAF differentiation [21]. Notably, these CAF subtypes are likely responsible for distinct functions for cancer progression, such as immunomodulatory functions and extracellular matrix (ECM) remodelling [19, 20]. These findings collectively imply that tissue environmental background and cancer-derived factors determine CAF complexity.

Diverse functions of CAFs in tumour progression have been reported. One substantial function of CAFs is as a source of various types of growth factors and chemokines, such as transforming growth factor-beta (TGF- β) [15, 22], CXC-chemokine ligand 12 (CXCL12)/SDF-1 [23], and HGF [24]. These CAF-derived factors promote an aggressive phenotype of cancer cells with invasive and metastatic behaviour, including the induction of EMT. The CD10 and GPR77 double-positive CAF subset secretes IL-6 and IL-8, sustaining cancer stemness and promoting chemoresistance [25]. In addition to direct effects on cancer cell behaviours, CAFs also generate VEGF to induce the angiogenesis of endothelial cells. CAFs also produce IL-6 and CXCL9 and regulate the immunosuppressive or immuno-promoting functions of inflammatory cells. The newly identified CAF subtype, antigen-presenting CAFs (apCAFs), can mediate CD4+ regulatory T-cell activation and CD8+ T-cell suppression [26]. These findings indicate that CAFs can mediate the function of both cancer cells and surrounding stromal cells within the TME.

Another essential function of CAFs is remodelling the extracellular matrix within the TME. CAFs produce ECM-related molecules, such as collagens and metalloproteases, which lead to the deposition and remodelling of the ECM. This remodelled ECM causes increased tissue stiffness, triggering proliferation signals in cancer cells. The increased tissue stiffness also promotes blood vessel collapse, reducing drug delivery. Matrix stiffening within tumour tissue also enhances the activation of YAP in normal fibroblasts and CAFs, which is involved in CAF generation and maintenance [27]. In addition, the metalloprotease produced by CAFs generates migratory tracks that allow cancer cell invasion [28]. Since CAFs can mediate the migration of cancer cells via E-cadherin/N-cadherin interactions [29], CAFs may be able to guide cancer cell invasion.

Cancer-derived EVs can dictate preferable CAF characteristics for cancer progression

Over the past few years, there has been an increasing number of reports regarding the functional interplay of EVs in communication between cancer cells and CAFs (Tables 1 and 2). In this review, to better understand the

intercellular crosstalk between cancer cells and CAFs via EVs, we focused on the papers that investigated EV components and revealed their functions on the recipient cells.

Many researchers have reported how CAFs are generated by cancer cells. Both direct contact and indirect interaction between cancer cells and CAFs are essential to maintain CAF characteristics. Among these interactions, TGF- β signalling is a well-established factor for activating fibroblasts and generating CAFs [2]. In addition to these mechanisms, cancer cells utilize EVs to generate CAFs (Fig. 1 and Table 1). The first report on cancer-derived EVs related to CAF induction was published by Webber et al., who showed that TGF- β was expressed on the surface of EVs derived from prostate cancer and mesothelioma cell lines [30, 31]. TGF- β on these cancer-derived EVs triggered the TGF- β /SMAD3 signalling pathway in recipient fibroblasts and induced myofibroblast-like phenotypes, including the expression of α -SMA and fibroblast growth factor 2 (FGF2) [30]. Recently, Huang et al. also showed that TGF- β in EVs generates CAFs via a noncanonical fibronectin-dependent pathway [32]. These reports demonstrated that EVs are responsible for some of the signalling previously thought to be carried out by growth factors. In studying triple-negative breast cancer, Sung et al. utilized an experimental model expressing integrin beta 4 (ITGB4) to determine the effect of EVs on the properties of CAFs [33]. Cancer-derived EVs transfer ITGB4 and induce BCL2 interacting protein 3 like (BNIP3L)-dependent mitophagy and glycolysis in CAFs. They also showed that the overexpression of ITGB4 in CAFs promotes breast cancer cell proliferation, EMT, and invasion [33]. Yan et al. demonstrated the reprogramming of glucose and glutathione metabolism in CAFs induced by miR-105 transferred by metastatic breast cancer cell-derived EVs [34]. Targeting of MX11 by miR-105 activates MYC, the essential driver of metabolic reprogramming in CAFs. Long non-coding RNAs (lncRNAs) are also transferred from cancer cells to fibroblasts. Since the exchange of metabolites and amino acids is one mechanism of interplay between cancer cells and CAFs [35–37], it is highly plausible that cancer cells utilize EVs to dictate metabolic reprogramming in CAFs and thus construct a preferable microenvironment for their progression.

Cancer cell properties such as TP53 gene mutation also affect EV components and have consequences on CAF generation [38–41]. Novo et al. demonstrated that TP53-mutant cancer cells mediate integrin trafficking in fibroblasts via EVs and promote the deposition of a pro-invasive ECM [38]. Although they did not focus on molecules encapsulated in EVs, this finding implies that EVs are involved in matrix remodelling within the TME via

Table 1 Cancer-derived EV functions on CAF generation and property

Contents of cancer-derived EVs		Tumour type	EV donor (From)		EV recipient (To)	Functions of EVs on the CAF properties	Reference
Proteins			From	To			
Integrins	Breast cancer Pancreatic cancer	Cancer cells	Cancer cells	CAFs		Up-regulates S100 gene expressions and promote cell growth and migration	[7]
TGF-β	Bladder cancer					Generate CAFs by activating SMAD-dependent pathway	[72]
Integrin αv and β1	Breast cancer					Integrin αv and β1 are enriched in CD63-positive EVs and induce CAF-like phenotypes in the fibroblasts. Galectin-3 might regulate the loading integrin αv and β1 in EVs.	[176]
ITGB4	Breast cancer					Induces BCL2 interacting protein 3 like (BNIP3L)-dependent mitophagy and glycolysis.	[33]
Sphingosine 1	Breast cancer					Sphingosine 1 derived from cancer cells may stimulate ERK-1/2 signalling and DNA synthesis	[73]
Survivin	Breast cancer					Generate CAFs with myofibroblastic features through inducing SOD1 expression to promote tumour proliferation and metastasis	[74]
Wnt2B	Cervical cancer					Generate CAFs through activating Wnt/β-catenin signalling	[75]
HSPC111	Colorectal cancer					Reprogramming lipid metabolism in CAFs to promote cancer metastasis.	[180]
TIMP-1	Colorectal cancer					Cancer-derived EVs transfer TIMP-1 to induced ECM remodelling in the fibroblasts.	[178]
LMP1	Epstein-Barr virus (EBV)-associated Nasopharyngeal carcinoma					Generate CAFs through NF-κB signalling and change aerobic glycolysis and autophagy in CAFs	[76]
PKM2	Gastric cancer					Generate CAFs by PKM2 nuclear translocation inducing NF-κB signalling	[77]
TGF-β	Head and neck squamous cell carcinoma					Generate CAFs through activation canonical TGF-β signalling pathway	[32]
PKM2	Hypoxic resistant lung cancer cells					Induce metabolic reprogramming in CAFs	[78]
IGF2	Liver cancer					Fluid shear stress-induced cancer cell medium promoted the activation and proliferation of CAFs via activating PI3K/AKT signaling pathway.	[172]
α-SMA	Lung cancer					Cancer-derived EV transfer α-SMA in both lung cancer cell line and fibroblasts. These EVs also promote cell proliferation and inhibit apoptosis.	[79]
TGF-β	Malignant ascite from gastric cancer and ovarian cancer					TGF-β in EVs may induce CAF phenotypes in peritoneal mesothelial cells	[80]

Table 1 (continued)

Contents of cancer-derived EVs	Tumour type	EV donor (From)	EV recipient (To)	Functions of EVs on the CAF properties	Reference
HSP90 and p-IKk α / β complex	Melanoma			Promote the proangiogenic capacity via activating NF- κ B signalling to induce CXCL1 expression in CAFs.	[173]
TGF- β	Mesothelioma cancer Bladder cancer			Triger the myofibroblast differentiation	[30]
FAP and EBV-encoded latent membrane protein 1 (LMP1)	Nasopharyngeal carcinoma			Generate CAFs via enhancing YAP1 signalling and increasing FAP expression.	[177]
COL6A1	Osteosarcoma			COL6A1-positive EVs generate CAFs expressing interleukins, α -SMA, and TGF- β	[81]
Gain-of-function p53	Ovarian cancer			Instigate CAF phenotypes in fibroblasts through the Nrf2-dependent pathway	[39]
Annexin A1	Pancreatic cancer			Induce myofibroblasts features in the fibroblasts and endothelial cells	[82]
Lin28B	Pancreatic cancer			Generate CAFs from pancreatic stellate cells through activating let-7/HMGA2/PDGFR β axis.	[83]
Hyal1	Prostate cancer			Stimulate fibroblast chemotaxis by the increased adhesion and activating FAK signalling.	[84]
TGF- β	Prostate cancer			Triger the myofibroblast differentiation and promote cancer growth and angiogenesis	[31]
C-terminal Dsg2	Squamous cell carcinoma			Dsg2-positive EVs activate Erk1/2 signalling and promote cell proliferation in fibroblasts.	[85]
Coding RNAs					
Inflammation-inducing mRNAs	Melanoma	From Cancer cells	To CAFs	Induce CAF subtype with inflammatory signatures in within metastatic niche	[47]
non-coding of transposable RNAs					
miR-105	Breast cancer	From Cancer cells	To CAFs	Reprogram glucose and glutamine metabolism to fuel adjacent cancer cells	[34]
miR-105 and miR-204	Breast cancer			Cancer-derived EVs might transfer miR-105 and miR-204 and suppress RAGC expression in fibroblasts.	[175]
miR-122	Breast cancer			Down-regulates glucose consumption of fibroblasts	[63]
miR-125b	Breast cancer			Generates CAFs from resident fibroblasts through targeting TP53INP1 expression	[43]
miR-130b-3p	Breast cancer			Generate CAFs via targeting SPIN90 in fibroblasts and facilitate cancer progression.	[179]

Table 1 (continued)

Contents of cancer-derived EVs	Tumour type	EV donor (From)	EV recipient (To)	Functions of EVs on the CAF properties	Reference
miR-185-5p, miR-652-5p, and miR-1246	Breast cancer			Three miRNAs in cancer-derived EVs can be involved in the induction of CAF phenotypes in normal fibroblasts.	[171]
miR-370-3p	Breast cancer			Induce fibroblast activation through CYLD/NF-κB signalling and promote cancer progression	[86]
Decreased miR-34c	Cholangiocarcinoma			Enhancing Wnt1 expression in fibroblasts and generate CAFs. miR-34 directly target Wnt1 expression.	[87]
miR-146a	Chronic lymphocytic leukaemia			Generate CAFs by targeting USPT6 expression in fibroblasts	[88]
miR-10a	Colorectal cancer (SW480 cell line)			Inhibit migration and expression of IL-6 and IL-8 expression in fibroblasts	[89]
miR-1249-5p, miR-6737-5p, and miR-6819-5p	Colorectal cancer			EVs derived from cancer cells with p53 shRNA generate CAFs. miRNAs in EVs may contribute to induction of CAF phenotype in fibroblasts.	[44]
miR-146a-5p and miR-155-5p	Colorectal cancer			Generate CAFs via targeting SOCS1 and ZBTB2 to activate JAK2-STAT3/NF-κB signalling. CXCL12/CXCR7 is associated with these miRNA expressions in cancer cells.	[181]
miR-200 family	Colorectal cancer			CRC cells with an epithelial phenotype but not a mesenchymal phenotype secrete miR-200 family members via EVs to attenuate TGF-β-mediated CAF features by targeting ZEB1 in normal fibroblasts.	[45]
miR-4534	Colorectal cancer			Suppress autophagy to induce CAF phenotypes in fibroblasts. EV miR-4534 targets ATG2B expression.	[182]
miR-27a	Gastric cancer			Generate CAFs to support cancer migration and invasion.	[90]
Several miRNAs including miR-193b	Gastric cancer			Induce CAF subtype with inflammatory signatures	[46]
miR-192, miR-215	Head and neck squamous cell carcinoma			Generate CAFs through targeting CAV1 to induce TGF-β/SMAD signalling	[91]
miR-9-5p	Head and neck squamous cell carcinoma			HPV-positive head and neck squamous cell carcinoma cells secrete miR-9-5p via EVs. EV miR-9-5p suppresses NOX4 expression to inhibit the induction of TGF-β-mediated CAF phenotype in fibroblasts.	[174]
miR-21	Hepatocellular carcinoma			Generate CAFs from hepatocyte stellate cells through activating PDK1/Akt signalling	[92]

Table 1 (continued)

Contents of cancer-derived EVs	Tumour type	EV donor (From)	EV recipient (To)	Functions of EVs on the CAF properties	Reference
miR-1247-3p	Hepatocellular carcinoma			Generate CAFs expressing inflammatory genes through targeting B4GALT3 to activate $\beta 1$ integrin/NF- κ B signalling	[49]
miR-181d-5p	Hepatoma cell			May induce CAF state via targeting SOCS3 expression in bone-marrow stem cells (BMSCs)	[93]
miR-3473b	Lewis lung carcinoma			Generate inflammatory gene expressing CAFs through activating NF- κ B signalling	[94]
miR-142-3p	Lung cancer			EVs derived from cancer cells with miR-142-3p over-expression generate CAFs via non-canonical TGF- β signalling	[96]
miR-210	Lung cancer			Generate CAFs expressing proangiogenic factors through activating JAK2/STAT3 signalling	[95]
lncRNA Gm26809	Melanoma			Generate CAF properties in NIH3T3 fibroblasts	[97]
miR-155	Melanoma			Generate CAFs expressing proangiogenic factors through inhibiting SOCS1 to activate JAK2/STAT3 signalling	[99]
miR-155 and miR-210	Melanoma			Increase aerobic glycolysis and decrease oxidative phosphorylation in fibroblasts.	[98]
miR-375	Merkel cell carcinoma			Generate CAFs through targeting RBPJ and p53 expression	[100]
miR-21	Mouse melanoma cell			Promote the invasion activity of fibroblasts through targeting TIMP-3 expression	[101]
lncRNA (lncRNA-CAF)	Oral squamous cell carcinoma			Stimulate IL-33 expression and CAF phenotypes in fibroblasts to influence CAF generation from other surrounding fibroblasts and promotes tumour growth	[102]
miR-630	Ovarian cancer			Generate CAFs through targeting KLF6 and activating NF- κ B signalling pathway	[103]
miR-155	Pancreatic cancer			Induce cancer-associated fibroblast like phenotype through repressing TP53P1	[104]
Several miRNAs including miR-1246 and miR-1268	Rhabdomyosarcoma			Rhabdomyosarcoma-derived EVs promote cell growth and stimulate angiogenic capacities in fibroblasts	[105]
Others		From	To		
Not investigated	Bladder cancer	Cancer cells	CAFs	Cancer-derived EVs induce inflammatory CAFs (ICAFs)	[48]
miR-1246, TGF- β , β -catenin, IL-6, p-STAT3	Colorectal cancer			Cancer-derived EVs generate CAFs. But the precise mechanism of how molecules in EVs induce CAF signatures in fibroblasts is not addressed.	[108]

Table 1 (continued)

Contents of cancer-derived EVs	Tumour type	EV donor (From)	EV recipient (To)	Functions of EVs on the CAF properties	Reference
Not investigated	Colorectal cancer			Stimulate migration capacity of CAFs via activating Rho-Fak signalling	[106]
Not investigated	Colorectal cancer			Cancer-derived EVs generate CAFs to acquire the capacity to invade matrix and to support cancer invasion.	[107]
Not investigated	Experimentally induced cancer stem cells (Pwll2-CSC)			Generate CAFs and enhance cell migration and invasion in CAFs.	[109]
Not investigated	Gastric cancer			Generate CAFs from pericytes through activating PI3K/AKT and MEK/ERK signalling pathways	[110]
Not investigated	Gastric cancer			Generate CAFs through canonical TGF-β signalling pathway	[111]
Not investigated	Lung cancer			Mediate immunomodulate effect via inducing PD-L1	[112]
Not investigated	Lung cancer			Cancer cells with TP53 mutation mediate the integrin trafficking in the fibroblasts via EVs and promote the deposition of invasive ECMs	[38]
Not investigated	Ovarian cancer			Cancer-derived EVs instigate cell adhesion and migration capacity in CAFs.	[67]
Not investigated	Prostate cancer			Cancer-derived EVs stimulate prometastatic factors including brain-derived neurotrophic factor and CXCL12.	[113]
Not investigated	Salivary adenoid cystic carcinoma			Induce the capacity to enhance cancer invasion and NGF expression in human periodontal ligament fibroblasts.	[114]

Table 2 CAF-derived EV functions on cancer cell property

Contents of CAF-derived EVs	Tumour type	EV donor (From)	EV recipient (To)	Functions of CAF-derived EVs on cancer progression	References
Proteins					
CD81	Breast cancer	From CAFs	To Cancer cells	Enhance cancer motility and metastasis through activating Wnt-planar cell polarity (PCP) signalling pathway	[50]
Extracellular matrix proteins and ADAM10	Breast cancer			Induce aldehyde dehydrogenase expression in cancer cells through Notch activation and enhance motility through the GTPase RhoA.	[115]
Wnt10b	Breast cancer			CAFs with low p85 α expression transfer Wnt10b via EVs and promote cancer progression.	[116]
Amphiregulin	Colorectal cancer			TGF- β -induced CAF model secrete Amphiregulin via EVs and promote cell proliferation in EGF-dependent patient derived organoids	[118]
Wnt3a	Colorectal cancer			Expansion of cancer stem cell to enhance chemoresistance	[117]
Sonic Hedgehog (Shh)	Esophageal squamous cell carcinoma			Promote cancer cell proliferation. CAF-derived EVs may transfer Shh to enhance tumour growth.	[119]
Annexin A6	Gastric cancer			Activate FAK-YAP signalling through stabilizing integrin β 1 to enhance drug resistance.	[120]
CD9	Gastric cancer			CAFs secrete CD-9 positive EVs and stimulate diffuse-type GC migration.	[51]
INHBA and THBS1/2	Gastric cancer			INHBA and THBS1/2 are associated with aggressive property of gastric cancer. HSF-1, master regulator of these molecules, may contribute to the loading of these molecules in MEF- and CAF-derived EVs.	[121]
Gremlin-1	Hepatocellular carcinoma			Promote EMT and sorafenib resistance via activating Wnt/ β -catenin signalling pathway.	[200]
SLPI	Ovarian cancer			Promote cancer progression by activating PI3K and MAPK signalling pathways.	[194]
TGF- β 1	Ovarian cancer			Promote EMT in cancer cells through inducing canonical TGF- β signalling.	[122]
Annexin A6	Pancreatic cancer			ANXA6- and CD9-double positive CAF-derived EVs facilitate p38 MAPK signal activation to enhance migratory ability in PDAC cells.	[52]
Galectin-1	Prostate cancer Pancreatic cancer Melanoma			CAF-derived galectin-1 may contribute to cancer migration.	[123]
Coding RNAs					
SNAIL mRNA	Lung cancer	From CAFs	To Cancer cells	Transfer SNAIL mRNA and promote EMT in cancer cells.	[124]
non-coding of transposable RNAs					
		From	To		

Table 2 (continued)

Contents of CAF-derived EVs	Tumour type	EV donor (From)	EV recipient (To)	Functions of CAF-derived EVs on cancer progression	References
LINC00355	Bladder cancer	CAFs	Cancer cells	Function as a sponge of miR-15a-5p and increase HMGA2 expression to promote cancer progression	[125]
LINC00355	Bladder cancer			Promote cancer cell proliferation.	[126]
Decreased miR-1-3p	Breast cancer			miR-1-3p expression is decreased in CAF-derived EVs. These CAF-derived EVs promote cancer progression. miR-1-3p targets GUS1 expression in cancer cells.	[133]
Decreased miR-4516	Breast cancer			miR-4516 expression is decreased in CAF-derived EVs and also promote cancer progression. miR-4516 targets FOSL1 to promote cancer progression.	[131]
Decreased miR-7641	Breast cancer			miR-7641 expression is decreased in CAF-derived EVs. These CAF-derived EVs can induce cancer stemness and metabolic reprogramming.	[132]
lncRNA SNHG3	Breast cancer			CAF-derived SNHG3 act as sponge for miR-330-5p expression to increase PKM protein expression results in metabolic reprogramming in cancer cells.	[62]
miR-16 and miR-148a	Breast cancer			FAK-null CAFs suppress cancer metastasis, and this CAF-derived EVs can partially contribute to the reduced tumour cell activities and metastasis.	[129]
miR-181d-5p	Breast cancer			Promote cancer cell migration and invasion through targeting CDX2 and HOXA5 to induce EMT in cancer cells.	[130]
miR-18b	Breast cancer			Promote cancer invasion and metastasis by targeting Transcription Elongation Factor A Like 7 (TCEAL7) expression in cancer cells.	[195]
miR-22	Breast cancer			CD63-positive CAF-derived EVs express miR-22 and promote Tamoxifen resistance in cancer cells through targeting SFRS1 expression.	[58]
miR-361 3-3p	Breast cancer			Promote cancer cell proliferation through targeting SOCS2 expression in cancer cells	[128]
miR-500a-5p	Breast cancer			Promote cancer proliferation and metastasis through targeting USP expression	[127]
miR-92	Breast cancer			Target directly the expression of LAT2 and induces PD-L1 expression through YAP activation in breast cancer cells.	[58]

Table 2 (continued)

Contents of CAF-derived EVs	Tumour type	EV donor (From)	EV recipient (To)	Functions of CAF-derived EVs on cancer progression	References
Non-coding of transposable RNAs	Breast cancer			Stimulate RIG-I recognition to activate STAT1 in cancer cells.	[53]
miR-1323	Cervical cancer			Promote radioresistance via targeting PABPN1 and activating Wnt/ β -catenin signalling pathway.	[198]
circN4BP2L2	Colorectal cancer			Promote cancer cell proliferation and metastasis. circN4BP2L2 in EVs targets miR-664b-3p to induce HMGB3 expression.	[188]
lncRNA CCAL	Colorectal cancer			Promotes Oxaliplatin resistance in CRC cells via stabilizing human antigen R (HuR) mRNA to increase β -catenin expression.	[56]
lncRNA H19	Colorectal cancer			Promote Cancer stemness and chemoresistance through targeting miR-141 expression and activating β -catenin signalling	[137]
lncRNA LINC00659	Colorectal cancer			Act as an RNA sponge for miR-342-3p expression to induce ANXA2 expression and promote EMT in cancer cells.	[142]
lncRNA SNHG3	Colorectal cancer			Promote cell proliferation via targeting miR-34b-5p to induce HOXC6 expression in cancer cell.	[196]
miR-135b-5p	Colorectal cancer			Promote tumour angiogenesis via targeting FOXO1 expression in cancer cell.	[189]
miR-135b-5p	Colorectal cancer			Might promote tumour angiogenesis and cancer cell proliferation via TXNIP expression.	[202]
miR-17-5p	Colorectal cancer			Promote cancer progression through targeting RUNX3 to activate MYC/TGF- β axis in cancer cells	[134]
miR-181-5p	Colorectal cancer			Promote 5-FU resistance via targeting neurocalcin δ (NCALD) expression in colorectal cancer cells.	[193]
miR-21	Colorectal cancer			Promote liver metastasis via transferring miR-21 and influence cell proliferation and chemoresistance.	[138]
miR-224-5p	Colorectal cancer			Involve in cancer progression through targeting SLC4A4 expression.	[141]
miR-24	Colorectal cancer			Enhance methotrexate resistance of cancer cells via targeting CDX2 to regulate HEPH expression.	[139]
miR-590-3p	Colorectal cancer			Promote the radioresistance in cancer cells through targeting CLCA4 to activate PI3K/AKT signalling pathway and reduce expressions of cleaved-caspase 3 and cleaved-PRAP.	[140]

Table 2 (continued)

Contents of CAF-derived EVs	Tumour type	EV donor (From)	EV recipient (To)	Functions of CAF-derived EVs on cancer progression	References
miR-92a-3p	Colorectal cancer			Promote cancer metastasis and chemotherapy resistance through targeting FBXW7 and MOAP1 expression	[136]
miR-93-5p	Colorectal cancer			Targeting FOXA1 and induce TGFβ3b and promote radioresistance	[135]
Decreased miR-320a	Endometrial cancer			miR-320a expression is decreased in CAF-derived EVs and promote cancer progression. miR-320a target HIF1α expression in cancer cells.	[143]
Decreased miR-148b	Endometrial cancer			miR-148b expression is decreased in CAF-derived EVs to enhance cancer metastasis through inducing EMT. miR-148b in EVs may targeting DNMT1 expression.	[144]
lncRNA NEAT1	Endometrial cancer			Act as an RNA sponge for miR-26a/b-5p expression to induce YKL-40 expression via STAT3 signalling and enhance cancer progression.	[145]
LINC01410	Esophageal cancer			Promote EMT via targeting miR-122 and inducing PKM2 expression.	[199]
miR-21	Esophageal squamous cell carcinoma			CAF-derived miR-21 cooperates with IL-6 to induce monocytic myeloid-derived suppressor cells (M-MDSCs), resulting in cisplatin resistance regulation in cancer cells.	[146]
Decreased miR-34	Gastric cancer			miR-34 expression is decreased in CAF-derived EVs and promote cancer progression.	[147]
lncRNA circ_0088300	Gastric cancer			Act as an RNA sponge for miR-1305 expression to promote cancer progression. KHDRBS3 contributes to circ_0088300 transfer via CAF-derived EVs.	[150]
miR-199a-5p	Gastric cancer			Promote cancer progression by targeting FKBP5 expression and activating mTORC1 signalling in cancer cells.	[201]
miR-522	Gastric cancer			Suppress ferroptosis via targeting ALOX15 expression and promote chemoresistance. hnRNPA1 and USP7 are associated with miR-522 secretion via CAF-derived EVs.	[148]
MMP-11 and Decreased miR-139	Gastric Cancer			Transfer MMP-11 to promote cancer cell progression. miR-139 expression is decreased in CAF-derived EVs and also promote cancer progression. miR-139 may target MMP11.	[149]

Table 2 (continued)

Contents of CAF-derived EVs	Tumour type	EV donor (From)	EV recipient (To)	Functions of CAF-derived EVs on cancer progression	References
Decreased miR-3188	Head and neck cancer			miR-3188 expression is decreased in CAF-derived EVs to promote cell proliferation and inhibit apoptosis in cancer cells. EV-derived miR-3188 targets BCL2 expression.	[151]
miR-196a	Head and neck cancer			Promote cisplatin resistance via targeting CDKN1B and ING5 expression.	[152]
Decreased miR-150-3p	Hepatocellular carcinoma			miR-150-3p expression is decreased in CAFs and their EVs to promote cancer cell progression.	[153]
Decreased miR-29b	Hepatocellular carcinoma			miR-29b expression is decreased in CAF-derived EVs and promote cancer migration and invasion. miR-29b may target DNMT3b to modulate EMT in cancer cells.	[154]
Decreased miR-320a	Hepatocellular carcinoma			miR-320a expression is decreased in CAF-derived EVs. These CAF-derived EVs promote cancer progression. miR-320a targets PBX1 expression in cancer cells.	[155]
Decreased let7a-5p	Lung cancer			Sulfonylurea receptor 1 (SUR1) expressing cancer cells decreased let-7a-5p expression in their EVs to induce CAFs. Mechanistically, let-7a-5p targets TGFBR1 to inactivate the TGF-β signalling in fibroblasts.	[184]
lncRNA OIP5-AS	Lung cancer			Export OIP-AS to suppress miR-142-5p and induce PD-L1 expression. EVs can be involved in immune tolerance of tumour.	[183]
lncRNA SNHG12	Lung cancer			Promote cisplatin resistance by binding to HuR to facilitate RNA stability and XIAP expression.	[187]
lncRNA TUG1	Lung cancer			Promote cancer cell migration, invasion, and glycolysis. TUG1 in EVs may target miR-524-5p to induce SIX1 expression.	[185]
miR-103a-3p	Lung cancer			Suppress apoptosis and promote cisplatin resistance through targeting Bak1 expression. Pum2 contributes to miR-103a loading into CAF-derived EVs.	[159]
miR-130a	Lung cancer			Cisplatin-induced miR-130a is transferred by CAF-derived EVs and promotes chemoresistance in cancer cells. PUM2 contributes to miR-130a packaging into CAF-derived EVs.	[158]
miR-20a	Lung cancer			Promote cancer cell proliferation and cisplatin resistance via targeting PTEN expression in non-small cell lung cancer cells.	[192]

Table 2 (continued)

Contents of CAF-derived EVs	Tumour type	EV donor (From)	EV recipient (To)	Functions of CAF-derived EVs on cancer progression	References
miR-210	Lung cancer			Promote cancer cell migration and invasion through targeting UPF1 to induce EMT in cancer cells	[156]
miR-369	Lung cancer			Promote cancer cell migration and invasion through targeting NF1 and mediate MAPK signalling pathway	[157]
miR-4717-5p	Malignant lymphoma			Induce gemcitabine resistance through targeting ENT2 expression in cancer cells.	[55]
Decreased miR-34a	Oral squamous cell carcinoma			Promote cancer cell proliferation and metastasis through AKT/GSK-3 β /catenin signalling. miR-34a can target AXL in cancer cells.	[161]
miR-382-5p	Oral squamous cell carcinoma			Promote cancer cell migration and invasion. miR-382-5p contributes to EV-mediated cancer progression.	[160]
miR-1228	Osteosarcoma			Promote cancer migration and invasion through targeting SCAI.	[162]
miR-21 isomiR	Ovarian cancer			Confer the chemo-resistance through targeting APAF1	[163]
miR-98-5p	Ovarian cancer			Promote cisplatin resistance via targeting CDKN1A.	[164]
miR-106b	Pancreatic cancer			Gemcitabine induce miR-106a in CAFs and their EVs. CAF-derived miR-106a can promote cancer cell proliferation.	[165]
miR-331-3p	Pancreatic cancer			Promote cancer progression via targeting SCARAS expression in PDAC cells.	[191]
miR-92a-3p, miR-181a-5p, miR-222-3p, miR-221-3p, miR-21-5p	Pancreatic cancer			CAF's might transfer miRNAs in PDAC cells via EVs and promote gemcitabine resistance. miR-92a-3p could target PTEN expression in PDAC cells.	[190]
miR-1290	Prostate cancer			Promote EMT and metastasis via targeting GSK3 β expression in cancer cell.	[197]
miR-146a-5p	Prostate cancer			Promote cancer metastasis. Treatment of Dihydrotestosterone (DHT) decreases miR-146a-5p in CAF-derived EVs and attenuate cancer promoting function.	[186]
miR-409	Prostate cancer			Promote epithelial-mesenchymal transition through repression of tumor suppressor genes such as Ras suppressor 1 and stromal antigen 2	[166]
miR-224-5p	Renall cell carcinoma			Contribute to cancer progression	[167]

Table 2 (continued)

Contents of CAF-derived EVs	Tumour type	EV donor (From)	EV recipient (To)	Functions of CAF-derived EVs on cancer progression	References
Metabolites mitochondrial DNA (mtDNA)	Breast cancer	From CAFs	To Cancer cells	Promote estrogen receptor-independent oxidative phosphorylation restore in cancer-stem like cells and increase self-renewal capacity in these cells.	[168]
Metabolites including amino acids and lipids	Prostate cancer			Affect the metabolic properties in prostate cancer cells	[60]
Others RN7SL1	Breast cancer	From CAFs	To Cancer cells	Acting as damage-associated molecular patterns (DAMPs) and activating RIG-I in the recipient cancer cells	[54]
Protein binding, serine-type endopeptidase activity, signalling receptor and protein kinase binding-related molecules	Oral squamous cell carcinoma			CAF-derived EVs promote cancer invasion and apoptosis.	[169]
miR-146a and Snail mRNA	Pancreatic cancer			Gemcitabine induce the secretion of miR-146 and Snail mRNA via EVs and regulate survival and proliferation in cancer cells.	[170]

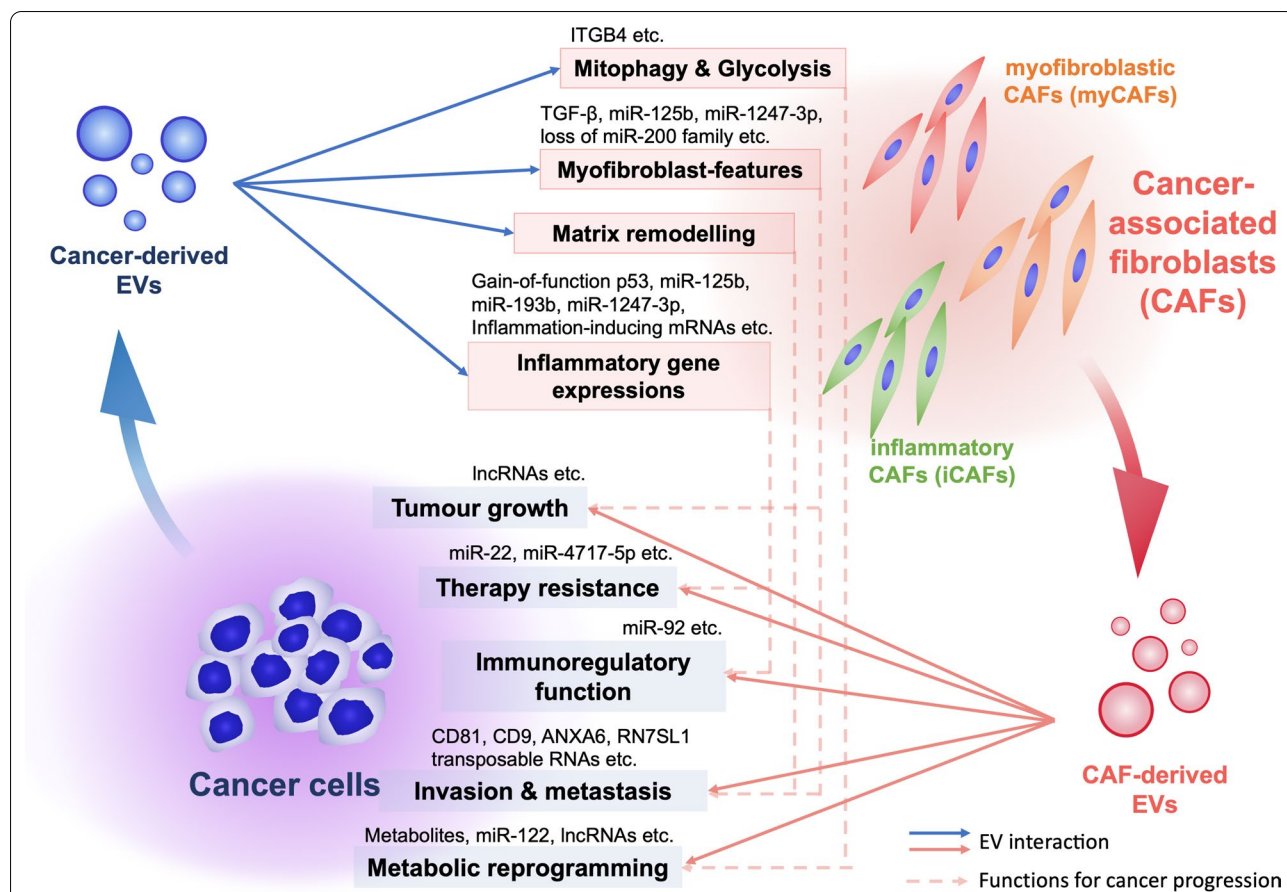


Fig. 1 Summary of the intercellular crosstalk between cancer cells and CAFs via EVs. The interplay between cancer cells and cancer-associated fibroblasts (CAFs) generates a unique tumour microenvironment (TME) that supports cancer progression. Cancer cells utilize EVs to modify surrounding cells within the tumour microenvironment. Cancer cells secrete various bioactive molecules in EVs, which are transferred into the surrounding fibroblasts and CAFs; such molecules include transforming growth factor-beta (TGF-β), ITGB4, p53, mRNAs and miRNAs (Table 1). These cancer-derived EVs confer specific phenotypes, such as mitophagy and glycolysis, myofibroblast features, matrix remodelling, and inflammatory gene expression (blue arrows), to support cancer progressions (broken arrows, the functions for cancer progression) (Table 1). Cancer-derived EVs also induce distinct CAF subtypes and contribute to the heterogeneity of CAFs. On the other hand, to support cancer progression, CAFs utilize EVs to transfer various functional molecules, such as CD81, CD9, FAP, miRNAs, lncRNAs, transposable RNAs and metabolites. These molecules confer aggressive phenotypes on cancer cells (red arrows). However, some molecules are downregulated in CAFs and thus their transfer to cancer cells is prevented (Table 2). Interestingly, specific CAF subtype-derived EVs are also involved in cancer progression, suggesting that EV content may differ among CAF subtypes

CAF generation and activation. Interestingly, Ma et al. showed the direct transfer of gain-of-function p53 proteins from cancer cells to fibroblasts via EVs. This gain-of-function p53 isoform induced a CAF phenotype in fibroblasts through the Nrf2-dependent pathway [39]. Since Nrf2 is the essential regulator of ECM production and deposition [42], transferring the gain-of-function p53 isoform to CAFs might involve a proinvasive ECM construction. In addition, Vu et al. found that miR-125b in breast cancer cell-derived EVs generates CAFs from resident fibroblasts [43]. Downregulation of TP53INP1 by EV-transferred miR-125b induced a CAF state in fibroblasts to promote tumour growth [43]. Given that aberrant p53 function can confer a

CAF phenotype on fibroblasts [38, 39, 44], the expression status of the TP53 gene in both cancer cells and CAFs may reflect the features of CAF subtypes. Recently, Bhome et al. demonstrated that the EMT phenotype of colorectal cancer (CRC) cells influences CAF generation [45] CRC cells with an epithelial phenotype secrete miR-200 family members via EVs to attenuate TGF-β-mediated CAF features by targeting ZEB1 in normal fibroblasts. However, EVs derived from CRC cells with a mesenchymal phenotype contain less miR-200 family, thus allowing TGF-β-mediated CAF feature induction. An aggressive subtype of CRC based on the consensus molecular subtypes (CMSs) is associated with mesenchymal gene signatures. Their study provides

one of the essential clues as to why cancer cells with aggressive phenotypes possess CAF-abundant stroma.

EVs also generate specific CAF subtypes from resident fibroblasts, promoting CAF heterogeneity. Our group reported that highly metastatic gastric cancer (GC) cells secrete EVs and induce the expression of chemokines such as IL-1 and IL-8 in stomach fibroblasts, which have similar properties as iCAFs [46]. Regarding the mechanism, these GC-derived EVs transport miRNAs, including miR-193b, to fibroblasts and induce chemokine expression. On the other hand, these GC cell-derived EVs do not have the capacity to regulate the expression of α -SMA and collagen, which are myCAF features. Notably, compared with GC cells with low metastatic potential, those with high metastatic potential can more strongly induce both α -SMA and chemokine expression in fibroblasts. These data suggest that cancer-derived EVs selectively confer iCAF-like features on fibroblasts. IL-8-expressing CAFs within the tumour stroma are closely associated with poor outcomes in patients with GC. These findings collectively imply that GC generates a protumorigenic microenvironment to support disease progression. Other research groups have also shown that cancer-derived EVs affect CAF heterogeneity [47, 48]. Goulet et al. showed that bladder cancer-derived EVs induce iCAF features in primary bladder fibroblasts [48]. Compared with TGF- β treatment, these cancer-derived EVs have a weaker effect on the induction of α -SMA in fibroblasts [48]. Although these researchers did not clarify the contribution of cancer-derived EVs to iCAF differentiation, they showed that EV-induced iCAFs express IL-6 and activate the STAT3 signalling pathway that leads to EMT in bladder cancer [48]. Lahav et al. demonstrated that metastatic melanoma cell-derived EVs activate proinflammatory signalling in fibroblasts within metastatic niches [47]. They also found that melanoma cell-derived EVs contain RNAs capable of instigating inflammatory signalling in fibroblasts, such as high-mobility group box 1 (Hmgb1), thymic stromal lymphopoietin (Tslp), and interferon regulatory factor 1 (Irf1) [47]. Interestingly, these EVs cannot induce myCAF features, suggesting that metastatic cancer cell-derived EVs may preferentially encourage iCAF features rather than myCAF features [49]. These findings indicate that EVs deliver messages from cancer cells, instigate various features in CAFs, and affect the feedback from CAFs for cancer progression.

CAF-derived EVs change the properties of cancer cells during disease progression

Stromal fibroblasts “educated” by cancer cells also secrete EVs and establish intercellular communication that ultimately benefits cancer progression (Fig. 1 and Table 2). Luga et al. first reported the functional role of CAF-derived EVs in cancer progression. They showed that

CD81-positive CAF-derived EVs activate the Wnt-planar cell polarity (PCP) signalling pathway and enhance breast cancer cell motility and metastasis [50]. CD81 on the surface of EVs may support the endocytic trafficking of Wnt11 in cancer cells. This mechanism mediated by CAF-derived EVs activates the Wnt-PCP pathway in cancer cells to drive invasive behaviour [50]. CD81, a tetraspanin family member protein, is a conventional marker of EVs [9]. Other tetraspanin family proteins may also support the internalization of CAF-derived EVs. Miki et al. showed that CAFs secrete CD9-positive EVs and stimulate diffuse-type GC migration. In addition, they showed that a CD9 neutralizing antibody inhibits EV uptake by GC cell lines [51]. Consistent with this finding, Nigri et al. also demonstrated that CD9 neutralizing antibody impaired CAF-derived ANXA6-positive uptake by PDAC cells [52]. ANXA6 can interact with CD9 in CAFs, suggesting that CD9 might regulate EV-specific ANXA6 shuttling. ANXA6- and CD9-double-positive CAF-derived EVs facilitate p38 MAPK signal activation to enhance migratory ability in PDAC cells. Although these reports did not clarify how the suppression of CD9 expression inhibits EV uptake in cancer cells, they identified CD9 function as a mediator of the internalization of CAF-derived EVs into cancer cells.

CAF-derived EVs support the development of cancer cell therapeutic resistance. Minn’s group reported the precise mechanisms by which breast cancer cells achieve therapeutic resistance through CAF-derived EVs [53, 54]. CAF-derived EVs contain transposable RNAs that stimulate RIG-I recognition to activate STAT1 in cancer cells. Activated STAT1 cooperates with juxtacrine-activated NOTCH3 to mediate NOTCH target gene transcription that supports resistance to chemotherapy and radiation [53]. They also found that NOTCH-MYC signalling induces RN7SL1 expression in CAFs. RN7SL1 generally possesses 5’ppp capping that is regulated by SRP9 and SRP14, which may prevent its recognition by RIG-I. However, NOTCH-MYC signalling in CAFs induces RN7SL1 without 5’ppp capping, which is encapsulated into CAF-derived EVs and acts as a damage-associated molecular pattern (DAMP) to activate RIG-I in recipient cancer cells [54]. Kunou et al. demonstrated the function of CAF-derived EVs in the gemcitabine resistance in malignant lymphoma [55]. These CAF-derived EVs suppress the expression of equilibrative nucleoside transporter 2 (ENT2) in lymphoma cells. They also found that miR-4717-5p is one of the most abundant miRNAs in CAF-derived EVs and directly targets ENT2 expression [55]. In colorectal cancer (CRC), Deng et al. showed that FAP-positive CAFs secrete lncRNAs via EVs [56]. These CAF-derived lncRNAs

promote oxaliplatin resistance in CRC cells in vitro and in vivo by stabilizing human antigen R (HuR) mRNA to increase β -catenin expression. The FAP-positive CAF subset is associated with regulatory T-cell-mediated immunosuppression, which results in poor outcomes in breast cancer patients [57]. Thus, it is possible that the FAP-positive CAF subset also secretes functional EVs to facilitate the malignant behaviour of cancer cells. Indeed, Dou et al. reported the immunomodulatory functions of CAF-derived EVs [58]. Although they did not refer to CAF subsets, they showed that CAF-derived miR-92 directly targets LATS2 expression and induces PD-L1 expression through YAP activation in breast cancer cells [58].

The functional role of CAF subset-derived EVs in cancer progression was recently reported. Gao et al. identified CD63-positive CAF subsets using single-cell analysis of oestrogen receptor α (ER α)-negative tumours in the MMTV-PyMT mouse mammary gland carcinoma model [59]. These CAF subsets secrete miR-22 via EVs to directly suppress the expression of ER α and PTEN in ER α -positive breast cancer cells and organoids, resulting in the induction of tamoxifen resistance. Interestingly, TIMP1, a CD63 ligand, can induce the STAT3 signalling pathway to regulate the expression of miR-22 and CD63 to generate a CD63-positive CAF phenotype. TIMP1 is upregulated in CD63-positive CAFs, suggesting a TIMP1-mediated positive feedback loop in the CD63-positive CAF phenotype. In addition, they showed that SFRS1 mediates miR-22 loading into CD63-positive CAF-derived EVs [59]. Although it is still unclear whether EV components differ among all CAF subsets, these findings indicate that CAF heterogeneity affects EV function in cancer progression.

Cancer-derived EVs reprogram energy metabolism in CAFs, as discussed in the previous section. CAFs also support the metabolic properties of cancer cells [60, 61]. Zhao et al. showed that CAF-derived EVs contain intact metabolites, such as amino acids, and change the metabolic properties of prostate cancer cells [60, 61]. Oxidative phosphorylation is inhibited in the presence of CAF-derived EVs. In contrast, glycolysis and lactate levels in prostate cancer cell lines are increased by these CAF-derived EVs. In addition to the direct transfer of metabolites via EVs, Li et al. also showed that the lncRNA SNHG3 affects the metabolic reprogramming of breast cancer cells. SNHG3 in EVs acts as a molecular sponge of miR-330-5p, resulting in increased lactate production in breast cancer cells [62]. Breast cancer-derived EVs transfer miR-122 and modify glucose consumption by fibroblasts at metastatic sites by targeting pyruvate kinases [63]. Moreover, metabolic dysregulation of CAFs may alter immunoregulation through IL-6 production [36].

Collectively, these findings imply that communication networks involving EVs contribute to cancer survival in environments with limited oxygen and nutrient supplies.

Perspectives on the therapeutic and diagnostic application of CAF-derived EVs

As described above, EV-mediated interactions between cancer cells and CAFs have been implicated in several malignant behaviours of cancer cells. Therefore, targeting EVs and CAFs is being explored as a fascinating strategy for cancer therapy. Kong et al. suggested that the inhibition of vitamin D receptor (VDR) signalling could target miR-10 secretion via EVs from CAFs and inhibit its cancer-promoting functions in PDAC [64]. This study was motivated by the two reports demonstrating that VDR signalling reprograms CAFs, thus diminishing their cancer-promoting role in PDAC, and is associated with better clinical outcomes in CRC [65, 66]. The inhibitory effects of two compounds on the interplay between cancer cells and CAFs have also been demonstrated. Lee et al. showed the impact of the multitarget small drug HNC0014 on the function of cancer spheroid-derived EVs. HNC0014 inhibits CAF generation by these EVs and may contribute to the antitumour immune response [67]. Chen et al. utilized ovatodiolide (OV), the bioactive component of *Anisomeles indica*, to suppress CAF generation and tumour sphere formation induced by cancer-derived EVs [68]. Interestingly, proton-pump inhibitors (PPIs), which are used to eradicate the oncogenic pathogen *Helicobacter pylori*, may also inhibit CAF generation [69].

Some studies have identified the molecules specific to CAF-derived EVs and these molecules have been proposed as diagnostic biomarkers for cancer. Ganig et al. performed proteome analysis of EVs derived from CAFs and normal fibroblasts and identified 11 proteins with differential abundance in CAF-derived EVs [70]. Among these candidate proteins, QSOX1 was selected for further study and was found to be decreased in CAF-derived EVs compared with normal fibroblast-derived EVs. The abundance of QSOX1 in plasma samples was reduced in CRC patients compared to healthy donors and patients with benign disease [70]. Although this study used small cohorts to investigate QSOX1 in EVs, the findings suggest the utility of CAF-derived EVs in cancer diagnosis. The secretome of fibroblasts influenced by cancer-derived EVs has also been investigated as a biomarker for lung cancer detection. Zhang et al. compared the secretome profile of lung cancer-derived EV treated and untreated MCR5 fibroblasts to find candidates for a diagnostic marker [71]. Based on the multiple datasets comprising 1897 patient samples, they showed that the gene expression signatures of five candidates are independent

prognostic factors for identifying patients who may require adjuvant therapy.

There remain challenges in the clinical application of EVs because of their diversity and the difficulty in selectively targeting cancer-associated EVs [8]. However, further investigations into targeting intercellular communication via EVs will provide several avenues for cancer therapy and diagnosis.

Conclusion

The precise mechanisms of intercellular communication between cancer cells and CAFs remain obscure because diverse pathways modulate multiple EV components and non-EV factors, such as growth factors, cytokines and chemokines. In addition, CAFs are surprisingly heterogeneous, which is the major obstacle to understanding their biology and developing related therapeutics. However, as described above, remarkable progress in EV research has led to the elucidation of the novel mechanism underlying the intrinsic cancer cell–stromal cell interplay during cancer initiation and progression. EVs derived from cancer cells and CAFs have impressively diverse functions that contribute to tumour progression. Cancer cells secrete EVs and thus dictate specific properties in CAFs. Against such “education” by cancer cells, CAFs “respond” via EVs to suppress cancer initiation and progression. Understanding the precise mechanisms of EVs in cancer cell–CAF interactions may provide breakthroughs in the development of diagnostic and prognostic tools and therapeutic strategies for cancer.

Abbreviations

CAFs: Cancer-associated fibroblasts; EVs: Extracellular vesicles; miRNAs: MicroRNAs; TME: Tumour microenvironment; MVBs: Multivesicular bodies; ESCRT: Endosomal sorting complex required for transport; BM-MSCs: Bone marrow-derived mesenchymal stem cells; α -SMA: Alpha-smooth muscle actin; EMT: Epithelial–mesenchymal transition; TGF- β : Transforming growth factor-beta; CXCL12: CXC-chemokine ligand 12; LIF: Leukaemia inhibitory factor; apCAFs: Antigen-presenting CAFs; ECM: Extracellular matrix; FGF2: Fibroblast growth factor 2; ITGB4: Integrin beta 4; BNIP3L: BCL2 interacting protein 3 like; B4GALT3: β -1,4-Galactosyltransferase III; lncRNAs: Long non-coding RNAs; PDAC: Pancreatic ductal adenocarcinoma; iCAFs: Inflammatory CAFs; myCAFs: Myofibroblastic CAFs; GC: Gastric cancer; Hmgb1: High-mobility group box 1; Tslp: Thymic stromal lymphopoietin; Irf1: Interferon regulatory factor 1; PCP: Planar cell polarity; DAMP: Damage-associated molecular pattern; ENT2: Equilibrative nucleoside transporter 2; CRC: Colorectal cancer; HuR: Human antigen R; ER α : Oestrogen receptor α ; VDR: Vitamin D receptor.

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