Molecular Cancer

REVIEW

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Cancer therapy resistance mediated by cancer-associated fibroblast-derived extracellular vesicles: biological mechanisms to clinical significance and implications

Zhengjun Lin[1,2†], Guoqing Li[1,2†], Ke Jiang[1,3], Zhihong Li[1*] and Tang Liu[1*]

Abstract

Cancer-associated fibroblasts (CAFs) are a diverse stromal cell population within the tumour microenvironment, where they play fundamental roles in cancer progression and patient prognosis. Multiple lines of evidence have identified that CAFs are critically involved in shaping the structure and function of the tumour microenvironment with numerous functions in regulating tumour behaviours, such as metastasis, invasion, and epithelial-mesenchymal transition (EMT). CAFs can interact extensively with cancer cells by producing extracellular vesicles (EVs), multiple secreted factors, and metabolites. Notably, CAF-derived EVs have been identified as critical mediators of cancer therapy resistance, and constitute novel therapy targets and biomarkers in cancer management. This review aimed to summarize the biological roles and detailed molecular mechanisms of CAF-derived EVs in mediating cancer resistance to chemotherapy, targeted therapy agents, radiotherapy, and immunotherapy. We also discussed the therapeutic potential of CAF-derived EVs as novel targets and clinical biomarkers in cancer clinical management, thereby providing a novel therapeutic strategy for enhancing cancer therapy efficacy and improving patient prognosis.

Keywords Cancer-associated fibroblasts, Extracellular vesicles, Therapy resistance, Clinical biomarker

Introduction

Cancer continues to be a serious public health challenge affecting people worldwide [1, 2]. Despite the substantial investment in cancer research and the extensive array of anti-cancer treatments available, therapy resistance remains the most serious factor impeding therapeutic efficacy [3, 4]. The intricate panorama of cancer therapy resistance entails multifaceted mechanisms such as altered drug uptake and efflux, inhibition of apoptosis signaling pathways, activation of cancer stem cells (CSCs), enhanced DNA repair capacities, disrupted cell cycle regulation, and physical obstacles impairing drug penetration and efficacy [5–7]. Nowadays, multiple ongoing studies have explored new drugs and combinations to address therapy resistance. For instance, bufalin, a compound found in secretions from the glands of toads

†Zhengjun Lin and Guoqing Li contributed equally to this work and share the first authorship.

*Correspondence:
Zhihong Li
lizhihong@csu.edu.cn
Tang Liu
liutang1204@csu.edu.cn
[1] Department of Orthopedics, The Second Xiangya Hospital, Central South University, 139# Middle Renmin Road, Changsha, Hunan Province 410011, China
[2] Xiangya School of Medicine, Central South University, Changsha 410013, Hunan Province, China
[3] Xiangya School of Pharmaceutical Sciences, Central South University, Changsha 410078, China

can effectively inhibit cancer progression and reverse various drug resistance mechanisms, supporting combining bufalin with standard therapies as a promising therapeutic strategy [8–11]. However, the complex molecular mechanisms behind cancer therapy resistance remain largely elusive. Notably, complex biological interactions between the tumour and tumour microenvironment have been confirmed as an essential factor that leads to cancer treatment failure. Multiple non-tumour cell types within tumour microenvironment interact closely with tumour cells and either positively or negatively mediate cancer therapy resistance [12, 13].

Cancer-associated fibroblasts (CAFs) are a major component of the stroma and are critically involved in the maintenance and reshaping of the extracellular matrix (ECM) [14, 15]. CAFs may originate from multiple cellular types, including quiescent tissue-resident fibroblasts, pancreatic or hepatic stellate cells, bone marrow-derived mesenchymal stem cells, endothelial cells, pericytes, and adipocytes [14, 16]. Multiple mechanisms have been confirmed to induce CAFs activation, including cancer cell-CAFs interacting signaling, ECM remodeling, oxidative stress, signals from other cells within the tumour microenvironment, cancer therapies, numerous tumor-inhibiting/promoting functions. Mechanistically, CAFs can regulate multiple tumour behaviours by secreting various cytokines, exosomes, and metabolites or by remodeling the structure and functions of the surrounding ECM [17, 18]. For instance, CAFs can produce TGFβ, fibroblast growth factor 5 (FGF5), and hepatocyte growth factor (HGF) to facilitate the invasion, proliferation, and therapy resistance of cancer cells [19]. On the contrary, CAFs can exert tumour-inhibiting functions by enhancing anticancer immunity, secreting pro-inflammatory cytokines, and producing certain ECM components as barriers to inhibit tumour cell invasion and dissemination [18] (Fig. 1).

Extracellular vesicles (EVs) are heterogeneous cell-derived membrane structures composed of exosomes and microvesicles that originate from the endosomal system or are shed from the plasma membrane, respectively [20, 21]. EVs harbor a rich cargo of molecules,

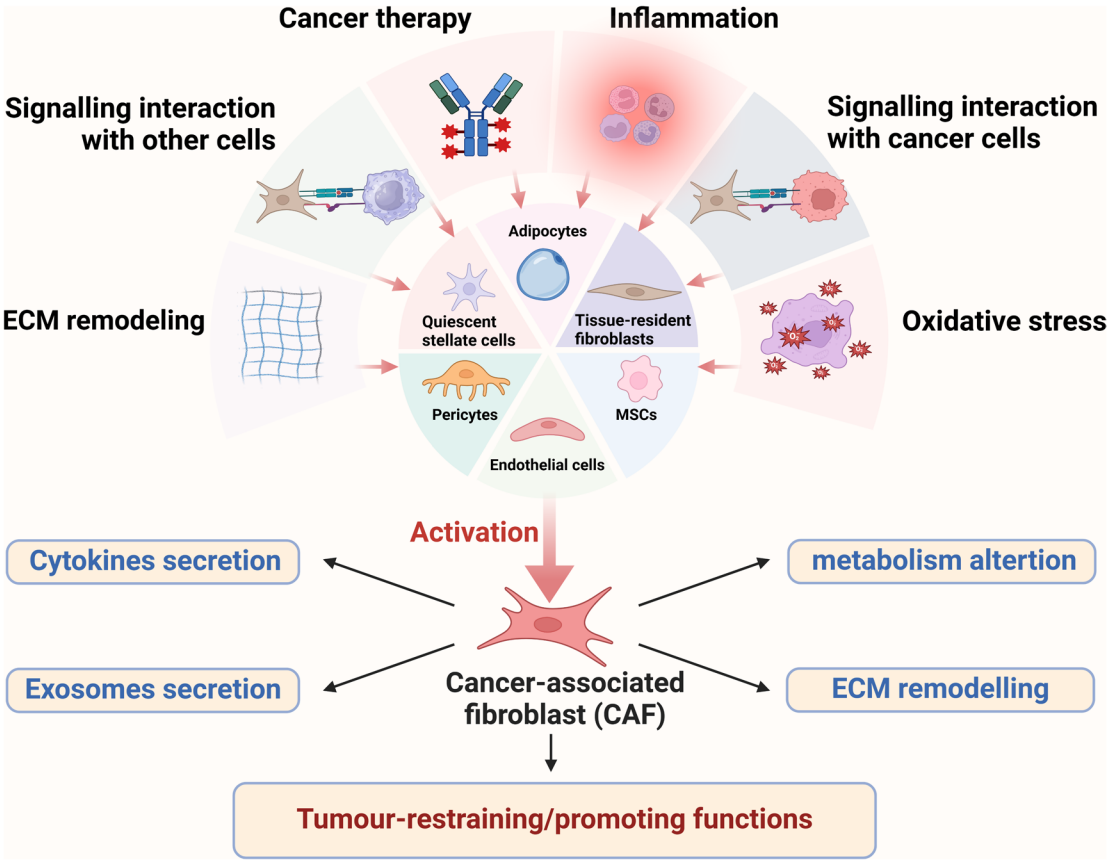


Fig. 1 Overview of CAFs. Potential cellular origins of CAFs include quiescent stellate cells, tissue-resident fibroblasts, mesenchymal stem cells (MSCs), endothelial cells, pericytes, and other cell types. CAFs can be activated by various mechanisms, including ECM remodeling, inflammation, oxidative stress and signalling interaction with cancer cells or other cells within tumour microenvironment. Activated CAFs can exert either tumour-restraining or tumour-promoting functions by secreting cytokines, exosomes, remodeling ECM and altering metabolism

including nucleic acids like DNA, mRNAs, and non-coding RNAs (ncRNAs), as well as lipids and diverse proteins. Functionally, EVs serve as vital mediators of intercellular communication, shuttling a plethora of molecules that regulate cellular processes in both normal and pathological contexts [22, 23]. Notably, multiple studies have highlighted the pivotal role of CAF-derived EVs in shaping the tumor microenvironment and influencing the development of various human cancers [24, 25]. For instance, CAF-derived EV-packaged PIAT can promote neural remodeling by enhancing the binding of YBX1 and PNI-associated mRNAs in a m5C-dependent manner in pancreatic cancer [26]. Intriguingly, CAF-derived EVs are implicated in mediating resistance to cancer therapies, including chemotherapy, targeted therapy, radiotherapy, and immunotherapy, indicating that CAFs and CAF-derived EVs can constitute a novel therapeutic target.

This review explores the crucial roles played by CAF-derived EVs in mediating resistance to cancer therapies and delves into the intricate mechanisms through which CAF-derived EVs bolster or undermine anticancer therapy resistance. Additionally, we discussed the prognostic value and therapeutic potential of CAF-derived EVs in cancer management.

CAF-derived EVs in cancer therapy resistance

Therapeutic resistance is a significant obstacle in enhancing cancer therapy efficacy and improving patient prognosis. Although multiple studies have proposed a conceptual framework of therapy resistance mechanisms, and novel therapeutic agents and combinational therapies have been developed to conquer the development of acquired therapy resistance, the complex biological mechanisms underlying cancer therapy resistance remain largely elusive. Hence, elucidating the detailed mechanisms of cancer therapy resistance and identifying novel therapy resistance-related biomarkers are critical for advancing personalized precision medicine and improving patient prognosis. Notably, ectopic alterations in CAFs and CAF-derived EVs have been found in the tumour microenvironment in various therapy-resistant cancers, indicating the role of CAF-derived EVs in cancer therapy resistance. The involvement of CAF-derived EVs in cancer resistance to chemotherapy, targeted therapy, radiotherapy and immunotherapy is summarized below (Table 1).

CAF-derived EVs in cancer chemotherapy resistance

As the first-line mode of anti-tumour treatment in multiple malignancies, multiple chemotherapeutic drugs with different properties and targets have exhibited prominent effectiveness. Nonetheless, both the inherent and acquired chemotherapy resistance take primary responsibility for treatment failure, adverse prognosis, and high recurrence rate. Multiple studies have demonstrated that CAF-derived EVs consisting of functional non-coding RNAs and proteins are critically involved in mediating cancer chemotherapy resistance through complex mechanisms and signaling pathways [27–30] (Fig. 2).

miRNAs

MicroRNAs (miRNAs) are about 21–23 nucleotides in length and function by binding to the 3' untranslated region of target mRNA, leading to mRNA degradation or translational repression [31]. CAFs can deliver diverse miRNAs to targeted cancer cells through EVs, thus regulating cancer therapy resistance. For instance, CAF-derived exosomal miR-130a has been confirmed to promote cisplatin (DDP) resistance in NSCLC, and the packing and secretion of exosomal miR-130a were regulated by the *PUM2* in CAFs [32]. Similarly, miR-20a was abnormally upregulated in NSCLC patient tissue samples and CAF-derived exosomes from NSCLC patients compared with normal tissues and NAFs from healthy paracancerous lung tissues, respectively. Functionally, CAF-derived exosomal miR-20a can promote tumour progression and DDP resistance by inhibiting *PTEN* and activating PI3K/AKT pathway in vivo and in vitro [33]. Monocytic myeloid-derived suppressor cells (M-MDSCs) have been found to correlate with DDP resistance in patients with ESCC, and CAFs can facilitate the differentiation of monocytes into M-MDSCs phenotypically and functionally in vitro. Mechanically, CAFs secreted IL-6 and exosomal miR-21 to promote M-MDSCs formation by stimulating the STAT3 signaling pathway, and CAFs-induced M-MDSCs promoted DDP resistance of ESCC cells [34]. In colon cancer, miR-24-3p transferred from CAFs to cancer cells through exosomes downregulated the expression of CDX2 and HEPN, inducing the methotrexate (MTX) resistance in both in vivo and in vitro experiments [35]. Taxanes are the first-line anti-tumor drugs for many malignant tumors via inhibiting microtubules, inducing inflammatory response and apoptosis, etc [36]. Both in vivo and in vitro experiments have revealed that CAF-derived exosomal miR-423-5p targeted 3'-UTR of *GREM2* to stimulate the TGF-β signaling pathway, thereby resulting in the therapy resistance to taxane in prostate cancer [37]. Sun et.al have reported that miR-296-3p, which was upregulated in activated CAFs-derived EVs from ovarian cancer, can promote ovarian cancer progression and paclitaxel resistance by regulating PTEN/AKT and SOCS6/STAT3 signaling pathways [38]. CAFs-derived exosomal miR-21 can also induce ovarian cancer paclitaxel resistance, migration, and invasion by directly targeting apoptosis protease activating fator1(*APAF1*) [39].

Table 1 CAF-derived EVs in cancer chemotherapy resistance

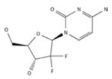
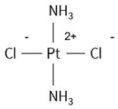
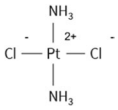
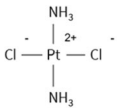
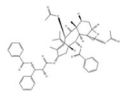
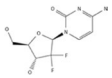
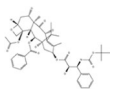
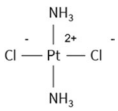
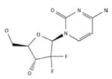
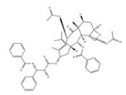
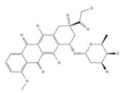
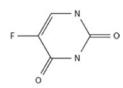
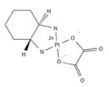
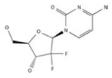
Key cargo	Cancer type	Genes and pathways or biological processes	Drug	Chemical structure	Drug resistance	Ref
miR-106b	PDAC	TP53INP1	GEM		↑	[29]
miR-130a	NSCLC	PUM2	DDP		↑	[32]
miR-20a	NSCLC	PTEN and PI3K/AKT	DDP		↑	[33]
miR-522	GC	ALOX15 and USP7/hnRNPA1	DDP and PTX	 	↑	[42]
miR-3173-5p	PDAC	ACSL4	GEM		↑	[43]
miR-432-5p	PC	CHAC1	DTX		↑	[44]
-	ESCC	RIG-I/IFN-β	DDP		↑	[46]
miR-146a	PDAC	Snail	GEM		↑	[50]
miR-148b-3p	BCa	PTEN and the Wnt/β-catenin	PTX and DOX	 	↑	[51]
miR-92a-3p	CRC	Wnt/β-catenin	5-FU/ OXA	 	↑	[52]
miR-21	PC	RAS/ATK/ERK axis	GEM		↑	[54]
miR-4717-5p	ML	ENT2	anti-pyrimidine		↑	[57]

Table 1 (continued)

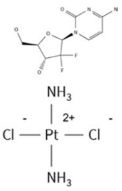
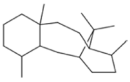
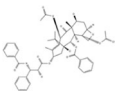
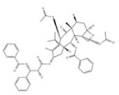
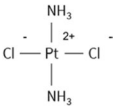
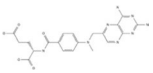
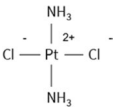
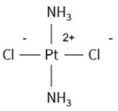
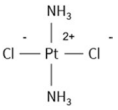
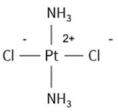
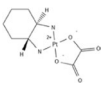
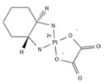
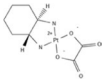
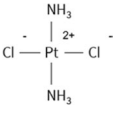
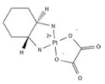
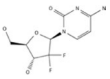
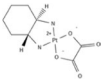
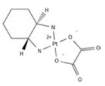
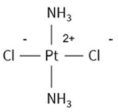
Key cargo	Cancer type	Genes and pathways or biological processes	Drug	Chemical structure	Drug resistance	Ref
miR-146a-5p	UBC	ARID1A and PRKAA2	GEM and DDP		↑	[59]
miR-423-5p	PC	GREM2 and TGF-β	Taxane		↑	[37]
miR-296-3p	OC	PTEN/AKT and SOCS6/STAT3	PTX		↑	[38]
miR-21	OC	APAF1	PTX		↑	[39]
miR-21	ESCC	STAT3	DDP		↑	[34]
miR-24-3p	CC	CDX2/HEPN	MTX		↑	[35]
miR-34c-5p	LSCC		DDP		↑	[60]
LINC00355	BCa	miR-34b-5p/ABCB1	DDP		↑	[62]
LncRNA UCAI	VSCC	miR-103a-WWE1 axis	DDP		↑	[64]
LncMEG3	SCLC	miR-15a-5p/CCNE1 axis	DDP		↑	[65]
LncFAL1	CRC	TRIM3 and Beclin1	OXA		↑	[66]
LncCCAL	CRC	HuR/β-catenin	OXA		↑	[67]
DACT3-AS1	GC	miR-181a-5p/ SIRT1	OXA		↑	[68]
circZFR	HCC	STAT3/NF-κB	DDP		↑	[70]

Table 1 (continued)

Key cargo	Cancer type	Genes and pathways or biological processes	Drug	Chemical structure	Drug resistance	Ref
CircN4BP2L2	CRC	PI3K/AKT/mTOR axis	OXA		↑	[71]
circFARP1	PDAC	LIF/STAT3 axis	GEM		↑	[72]
circBIRC6	PDAC	XRCC4	OXA		↑	[73]
FOSL1	CRC	ITGB4	OXA		↑	[74]
VEGFA	CRC		DDP		↑	[76]

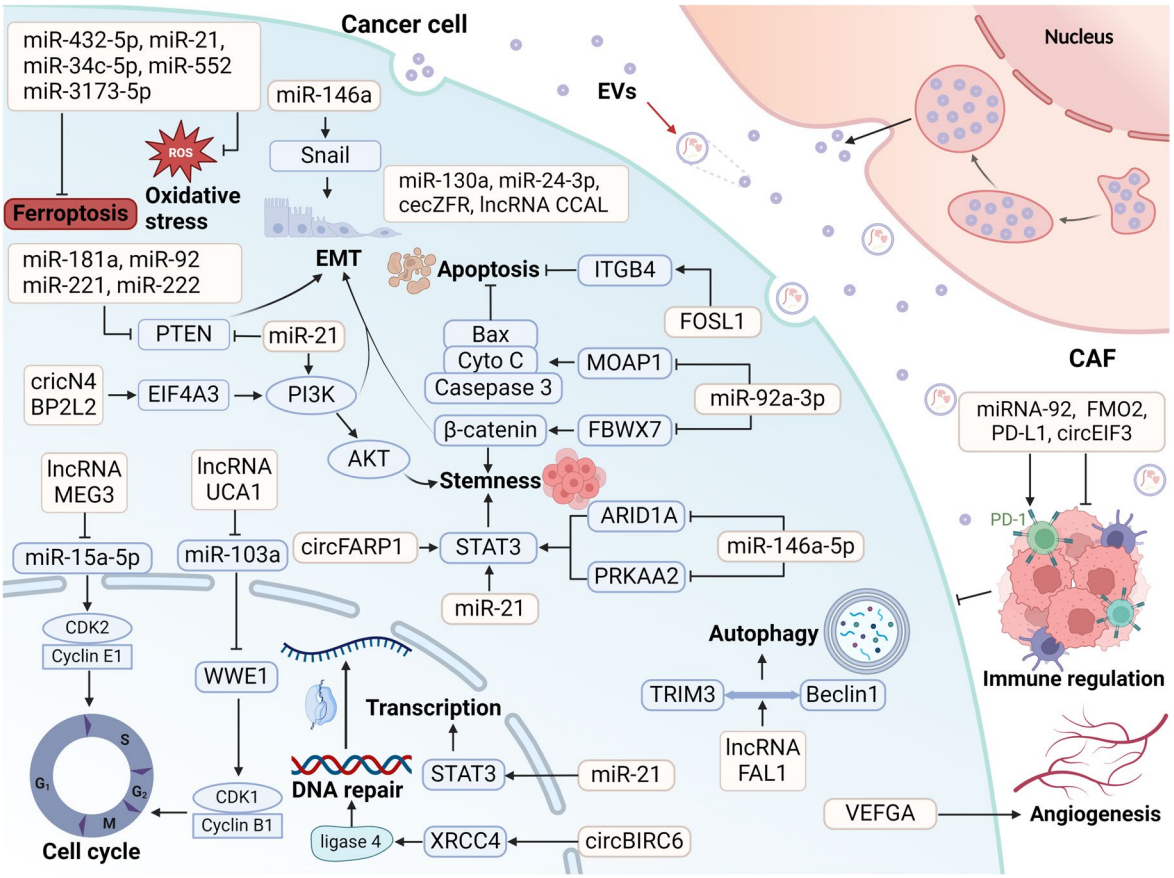


Fig. 2 CAF-derived EVs in cancer chemotherapy resistance. The detailed biological mechanisms of CAF-derived EVs in mediating cancer chemoresistance are summarized. CAF-derived EVs can deliver miRNAs, lncRNAs, circRNAs and proteins to mediate cancer chemotherapy resistance by regulating cell cycle, DNA repair, oxidative stress, EMT, apoptosis, autophagy, cancer cell stemness, angiogenesis, immune cells infiltration and various signalling pathways including PI3K/AKT, Wnt/β-catenin, and PTEN/mTOR pathways

Ferroptosis is a novel form of regulated cell death that involves iron-dependent lipid-ROS accumulation [40]. Ferroptosis has been identified as an important regulator of cancer therapy resistance, and inducing ferroptosis is a novel therapeutic strategy to reverse drug resistance [41]. Zhang et al. have isolated serum exosomes from gastric cancer patients and normal controls by ultracentrifugation, and found that the expression level of miR-552 was abnormally elevated in both tumour tissues and serum exosomes of gastric cancer patients. Further investigation has reported that DDP and paclitaxel treatment can induce CAFs to secret exosomal miR-552 by activating the USP7/hnRNPA1 axis in gastric cancer. Meanwhile, CAF-derived exosomal miR-552 can impair chemosensitivity by inhibiting ferroptosis by suppressing *ALOX15* [42]. Similarly, Qi et al. have obtained normal fibroblasts and CAFs from normal paracancerous pancreatic tissues and PDAC tumors respectively, and isolated normal fibroblast- and CAF-derived exosomes by ultracentrifugation. CAF-derived exosomes can inhibit ferroptosis in pancreatic cancer cells after gemcitabine (GEM) treatment in a non-contact co-culture system in vitro. Besides, miR-3173-5p was upregulated in co-induced CAF-derived exosomes and tumor tissues after GEM treatment. The mechanical investigation suggested that CAF-derived exosomal miR-3173-5p facilitated GEM resistance and suppressed ferroptosis by directly targeting *ACSL4 in vivo* and in vitro [43]. In prostate cancer, CAF-derived exosomal miR-432-5p reduces lipid peroxidation stress and inhibits ferroptosis by targeting *CHAC1*, thereby conferring docetaxel (DTX) resistance [44].

Evasion of apoptosis has been regarded as a major cause of cancer chemoresistance [45]. In esophageal squamous cell carcinoma (ESCC), CAF-derived exosomes decreased the chemotherapy sensitivity of DDP and inhibited ESCC cell apoptosis via the RIG-I/IFN-β signaling in vivo and in vitro [46]. Pancreatic fibroblasts have exhibited innately chemoresistant to GEM, and co-culturing PDAC cells with CAFs improved PDAC proliferation capability and reduced GEM-induced cell apoptosis by establishing a three-dimensional organoid-fibroblast co-culture system [47]. Simultaneously, miR-106b was upregulated in GEM-treated CAFs and CAF-derived exosomes, and exosomal miR-106b possessed the potential to promote acquired resistance to GEM via binding to Tumor protein p53-inducible nuclear protein 1 (*TP53INP1*) [29]. Korc et al. have isolated GEM-treated CAF-derived exosomes by ExoQuick-TC™ and microRNA-Seq was conducted to select differentially expressed miRNAs. The abnormal upregulation of a total of five miRNAs (miR-21, miR-181a, miR-221, miR-222, and miR-92a) was detected in GEM-treated CAF-derived exosomes, and these exosomal miRNAs may confer GEM resistance by directly targeting *PTEN* [48].

Epithelial-mesenchymal transition (EMT) plays multifaceted roles in cancer progression, metastasis, and therapy resistance, and targeting the EMT process and EMT transcription factors, e.g. ZEB, TWIST and SNAIL has become promising approaches to reverse therapy resistance [49]. GEM treatment can induce CAFs to secret more miR-146a and the specific promoter binding transcription factor of miR-146a, *Snail*, subsequently inducing EMT and chemoresistance to GEM in vitro [50]. CAF-derived exosomal miR-148b-3p has been demonstrated to induce the chemoresistance to PTX and DOX through inducing EMT by directly targeting *PTEN* and the Wnt/β-catenin pathway in bladder cancer, whereas the downregulation of miR-148b-3p and expression of *PTEN* could reverse the chemoresistance via the Wnt/β-catenin pathway [51]. 5-FU/L-OHP has a prominent chemotherapy effect on colorectal cancer (CRC). Hu et al. have isolated normal fibroblast- and CAF-derived exosomes by ultracentrifugation, and found that CAF-derived exosomes can facilitate invasion, metastasis, and chemotherapy resistance in CRC. miRNA microarray assay revealed that miR-92a-3p was significantly upregulated in CAFs and CAF-derived exosomes, and exosomal miR-92a-3p secreted by CAFs has been found to promote EMT, cell stemness, 5-FU/L-OHP resistance, and suppress mitochondrial apoptosis of CRC cells in vivo and in vitro. Mechanically, exosomal miR-92a-3p directly activated the Wnt/β-catenin signaling pathway and inhibited the expression of *FBXW7* and *MOAP* [52].

Oxidative stress is an adverse condition for cancer cells survival, whereas the hypoxic microenvironment is one of the key factors that promote cancer progression and facilitate therapy resistance [53]. In pancreatic cancer, hypoxia-induced CAFs can secret miR-21 abundant extracellular vesicles to promote pancreatic cancer cell stemness and GEM resistance [54]. Mechanically, the hypoxic microenvironment induced miR-21 secretion through HIF-1α activation, and miR-21 conferred resistance to GEM by activating the RAS/ATK/ERK axis [54]. Aerobic glycolysis is a typical phenotype of cancer cells, and glycolysis is also a determinant of cancer chemoresistance [55, 56]. In malignant lymphoma, CAF-derived exosomes can support the survival of lymphoma cells by promoting glycolysis, and inhibition of exosome secretion by RAB27B suppression inhibits the survival of lymphoma cells. Besides, CAF-derived exosomal miR-4717-5p can induce anti-pyrimidine drug resistance by directly targeting *ENT2* in lymphoma [57]. Cancer stem cells have been identified as a critical factor for tumor growth, chemoresistance, and recurrence, and tackling stemness-associated chemoresistance may

be an effective therapy approach [58]. In urothelial bladder cancer (UBC), CAF-derived exosomal miR-146a-5p can facilitate cancer stem cell niche formation, UBC cell stemness, and resistance to GEM and DDP by directly targeting the 3'UTR of mRNAs of *ARID1A* and *PRKAA2*. Mechanically, the downregulation of *ARID1A* can suppress the expression of *SOCS1* and activate the STAT3 signaling pathway, and downregulated *PRKAA2* can activate the mTOR signaling [59]. In vivo study has demonstrated that CAF-derived exosomal miR-34c-5p reduced the DDP resistance and stemness of laryngeal squamous cell carcinoma (LSCC) [60].

LncRNAs

LncRNAs are ncRNAs that are longer than 200 nt without protein-coding potential [61]. Multiple studies have indicated that CAF-derived exosomal lncRNAs can interact with multiple miRNAs in cancer cells to mediate chemoresistance. For instance, exosomal LINC00355 secreted by CAFs promoted DDP resistance by sponging miR-34b-5p to upregulate *ABCB1* in bladder cancer [62]. Intriguingly, the LINC00355/miR-34b-5p axis was also involved in facilitating EMT and the chemoresistance to DDP, OXA, and 5-FU in CRC [63]. Correspondingly in vulvar squamous cell carcinoma (VSCC) cells, exosomal lncRNA UCAI from CAFs can induce DDP resistance via the miR-103a-*WWE1* axis [64]. Exosomal lncMEG3 was secreted and transferred from CAFs to SCLC cells and induced DDP chemoresistance by targeting the miR-15a-5p/*CCNE1* axis [65]. Simultaneously, lncRNAs can alter the sensitivity of cancer cells to chemotherapeutic drugs depending on the no-miRNA binding pathways. Beclin1 was a crucial factor during OXA-mediated autophagic cell death in CRC cells. CAF-derived exosomal lncRNA FAL1 has been found to act as the scaffold that promoted the interaction between Beclin1 and TRIM3 and induced the TRIM3-dependent Beclin1 polyubiquitination, resulting in inhibition of autophagy and chemoresistance to OXA [66]. LncRNA CCAL in CAF-derived exosomes has been confirmed to confer OXA resistance by interacting directly with mRNA stabilizing protein HuR (human antigen R) to increase β-catenin mRNA and protein expression [67]. Downregulation of DACT3-AS1 was significantly with worse prognosis of GC patients. CAF-derived exosomal DACT3-AS1 elevated the oxidative stress level through miR-181a-5p/SIRT1-mediated ferroptosis, enhance the sensitivity to OXA of GC cells [68].

CircRNAs

In addition to miRNAs and lncRNAs, CAFs-secreted circular RNAs (circRNAs) also take a novel role in the development of both inherent and acquired chemoresistance. CircRNAs are a type of non-coding RNA that forms a covalently closed continuous loop structure [69]. For instance, circZFR was highly expressed in DDP-resistant HCC cell lines, CAFs, and CAF-derived exosomes. In vitro and in vivo studies further indicated that CAFs-secreted exosomal circZFR enhanced the DDP resistance of HCC cells by inhibiting the STAT3/NF-κB pathway [70]. As a third-generation platinum drug, OXA plays a prominent role in cancer therapy. CircN4BP2L2 secreted by CAFs could positively bind to *EIF4A3* to stimulate the PI3K/AKT/mTOR axis, correspondingly inducing the resistance to OXA in CRC [71]. In PDAC, CAF-derived exosomal circFARP1 also contributed to PDAC cell stemness and GEM resistance via the LIF/STAT3 axis [72]. Researchers have isolated and purified EVs from the plasma of PDAC patients by EV isolation kit, and detected that circBIRC6 was upregulated in plasma EVs and primary tumor tissues of oxaliplatin-resistant patients. Mechanically, circBIRC6 from CAF-derived EVs can directly bound to *XRCC4*, which encoded DNA ligase IV and elevated the crosstalk between *XRCC4* and Small Ubiquitin Like Modifier 1 (*SUMO1*) in PDAC. Consequently, non-homologous end joining (*NHEJ*) dependent DNA repair was activated, resulting in the resistance to oxaliplatin [73].

Proteins

Proteins are also an important part in CAFs-secreted EVs, and multiple CAFs-secreted exosomal proteins also serve a pivotal role in cancer progression and therapy resistance. For instance, FOSL1 was enriched in CAFs-secreted exosomes and was transmitted to CRC cells, thus conferring resistance to OXA of CRC cells by transcriptionally activating integrin β4 (*ITGB4*) [74]. Vascular Endothelial Growth Factor A (VEGFA) can induce the proliferation and migration of vascular endothelia cell and is involved in tumor angiogenesis [75]. Intriguingly, VEGFA was elevated in exosomes derived by CAFs isolated from DDP-resistant CRC tissues. Functionally, CRC cells exhibited enhanced viability and DDP resistance after CAF-derived exosomal VEGFA treatment [76] (Table 1).

CAF-derived EVs in cancer targeted therapy resistance

Targeted therapy involves corresponding therapeutic drugs for targeting and inhibiting driver mutations that are characteristic of certain types of cancer [77, 78]. Multiple targeted therapy drugs have been applied in the treatment of diverse cancers, such as claudiximab for gastric cancer, TKIs for lung cancer and colorectal cancer, and trastuzumab targeting HER-2 for breast cancer [79]. However, the greatest obstacle to targeted cancer therapy is the inevitable emergence of drug resistance, which

contributes to therapeutic failure and ultimate patient demise in genotype-matched precision medicine [80]. Multiple studies have indicated that EMT is connected with cancer progression and targeted therapy resistance [81]. It has been identified that CAF-derived EVs were involved in EMT induction through several biological processes including ECM remodeling, metabolic reprogramming, and oncogenic pathways activating [82]. In HCC, CAF-derived protein SPP1 was able to induce TKIs (sorafenib and lenvatinib) resistance. Mechanically, SPP1 induced EMT by activating the phosphorylation of the RAF/MAPK axis and PI3K/AKT/mTOR axis through the PKCα signalling pathway [83]. Similarly, Gremlin-1 from CAF-derived exosomes was proved to have an active role in regulating the EMT process and reducing the sensitivity of HCC cells to sorafenib via Wnt/β-catenin and BMP signaling pathways. Clinically, patients with HCC exhibited a higher exosomal gremlin-1 level in serum, and serum gremlin-1 level could predict the sorafenib response of HCC patients [84]. In addition, CAFs-secreted CXCL12 conferred sorafenib resistance in HCC cells by upregulating *FOLR1* expression in the mRNA level, and the CXCL12/CXCR4/FOLR1 was involved in sorafenib resistance of HCC [85]. Moreover, the in vitro experiment has demonstrated that miR-1228-3p carried by CAF-derived exosomes conferred sorafenib resistance in HCC9724 cells by modulating the PLAC8/PI3K/AKT axis [86]. Gao et al. have identified that CD63 + CAFs, a new CAF subset, can promote ERα downregulation and tamoxifen resistance in breast cancer by single-cell sequencing. Mechanically, CD63 + CAFs can secrete exosomal miR-22 to induce tamoxifen resistance by directly targeting ERα and PTEN. Furthermore, the packaging of miR-22 into CD63 + CAF-derived exosomes was regulated by SFRS1, and CD63 stimulated STAT3 to maintain the phenotype and function of CD63 + CAFs. Inspiringly, the pharmacological inhibition of CD63 + CAFs with a CD63-neutralizing antibody or cRGD-miR-22-sponge nanoparticles can effective reverse tamoxifen resistance in breast cancer [87].

CAF-derived EVs in cancer radiotherapy resistance

Radiotherapy is one of the mainstays of cancer treatment, and radiotherapy is widely used in the treatment of multiple malignancies, such as anaplastic thyroid cancer (ATC), and ESCC [88, 89]. Approximately half of cancer patients will receive radiotherapy either alone or in combination with other therapies during their treatment [90]. However, radioresistance is still a critical challenge resulting in radiotherapy failure, cancer relapses, and poor prognosis in clinical practice [91]. Recent work has indicated that radiation can mediate the contents and secretion of functional exosomes from cancer cells and other cell types within tumor microenvironment, resulting in radiotherapy resistance and radiation-induced bystander effects [92, 93]. For instance, exosomal miR-143-3p has been estimated to confer radiation resistance by inducing M2 macrophage polarization in locally advanced ESCC [94]. CSCs in tumours are mostly resistant to conventional therapies including ionizing radiation, and a high dose of radiation is required to eradicate CSCs. CAF-derived exosomes promoted radiotherapy resistance through enhancing CRC stemness by activating TGF-β signalling pathway [95]. Chen et al. have isolated and purified exosomes from the plasma of CRC patients by ExoQuick Exosome Precipitation Kit, and detected that miR-590-3p was upregulated in patients with radioresistance compared with patients with radiosensitivity. Besides, ectopic upregulation of miR-590-3p was detected in CAF-derived exosomes compared to normal fibroblast-derived exosomes, and CAF-derived exosomal miR-590-3p decreased CRC sensitivity to radiation. Mechanically, miR-590-3p inhibited the expression of *CLCA4* and mediated the phosphorylation of PI3K and AKT in CRC cells [96]. Similarly, both in vitro and in vivo studies have demonstrated that miR93-5p was also transferred by exosomes from CAFs to CRCs, and CAF-derived exosomal miR-93-5p downregulated *FOXA1* and reversed the suppression of *FOXA1* on *TGFB3*, subsequently contributing to radiation resistance [97]. In lung cancer, in vitro experiment has revealed that CAFs derived exosomal miR-196a-5p was upregulated and induced radioresistance by sponging *NFKBIA* and activating the NF-κB signalling pathway [98]. FAP-positive CAFs, a specific CAF subpopulation in ESCC have been found to transfer exosomal lncRNA AFAP1-AS1 to ESCC cells, and AFAP-AS1 promoted the repairment of damaged DNA, conferring radiotherapy resistance of ESCC cells [99] (Table 2).

CAF-derived EVs in cancer immunotherapy resistance

Immunotherapy has ushered in a new era of cancer treatment and altered the therapeutic landscape for multiple human malignancies [100, 101]. The clinical goal of cancer immunotherapy is to prime the host immune system to provide passive or active immunity against malignant tumors [102, 103]. Rather than merely enhancing overall immunity, immunotherapy is also involved in the improvement of tumour immune microenvironment, potentially providing prolonged survival for cancer patients [104]. Various immunotherapies, including immune checkpoint inhibitors (ICIs), such as anti-PD-L1 drugs nivolumab and pembrolizumab, chimeric antigen receptor (CAR) T cells, tumor vaccines, and adoptive cell transfer (ACT), have shown promising curative effect on multiple cancers [105–108]. Despite

Table 2 CAF-derived EVs in cancer radiotherapy resistance

Key cargo	Cancer type	Genes and pathways or biological processes	Radioresistance	Ref
miR-143-3p	ESCC	M2 macrophage polarization	↑	[94]
miR-590-3p	CRC	PI3K and AKT	↑	[96]
miR-93-5p	CRC	FOXA1 and TGFB3	↑	[97]
miR-196a-5p	LC	NFKBIA and NF-κB	↑	[98]
lncRNA AFAP1-AS1	ESCC	DNA repairment	↑	[99]

tumour immunotherapy being approved for clinical use and achieving unprecedented results, resistance remains an obstacle to the application of immunotherapies [109]. Multiple studies have identified that CAFs were involved in mediating tumour immunotherapy resistance through immunosuppressive microenvironment generation, immune cell exclusion, and phenotype alternation [18]. For instance, signal-cell analysis revealed different CAF clusters, among which the cluster 0 CAFs (CAFs associated with ECM remodeling, collagen formation, and cell adhesion) upregulated the expression of PD-1 and cytotoxic T-lymphocyte associated protein 4 (CTLA4) on Treg cells, which, in turn, inhibited T cells function and induced immune resistance [110]. In breast cancer, CAFs inhibited ICIs efficiency by suppressing CD8 + T cell infiltration [111]. In HCC, prominent CD36 + CAFs exhibited high-level lipid metabolism and mediated macrophage migration inhibitory factor (MIF) expression by activating lipid peroxidation/p38/CEBPs axis. CD36 + CAFs also recruited CD33 + MDSCs, altering the tumour immune microenvironment [112]. CAF-derived EVs also play a critical role in regulating cancer immunotherapy resistance. For instance, CAF-derived exosomal miR-92 can significantly promote T cell apoptosis and confer immunotherapy resistance of breast cancer cells. Mechanically, miRNA-92 specifically bound to *LATS2*, which further interacted with *YAP1*, and chromatin immunoprecipitation confirmed that *YAP1* could bind to the enhancer region of PD-L1 after nuclear translocation, promoting transcriptional activity [113]. CAFs can influence the efficacy of immunotherapy by interfering with the cytotoxic effects of T cells. In melanoma, studies have found that hypoxia can induce the secretion of immunosuppression factors such as TGF-β, VEGF, and PD-L1 from CAFs, which exerted an inhibitory effect on T cell-mediated cytotoxicity [114]. In CRC, the hypoxic microenvironment induced the production and excretion of circEIF3K-containing exosomes from CAFs compared with normoxic CAFs. CircEIF3 can reduce miR-214 to upregulate the expression of PD-L1, thereby inducing CRC cell proliferation, migration, metastasis, and immune escape [115]. In epithelial ovarian cancer (EOC), CAF-derived protein FMO2 facilitated the infiltration of lymphocytes. Higher level FMO2 was associated with worse prognosis in patients with similar levels of immune checkpoints such as PD-1 and PD-L1 suggesting that FMO2 could be a biomarker for predicting immunotherapy sensitivity [116]. In addition, it has been demonstrated that the CAF-derived EVs could mediate the immune escape of UBC by promoting PD-L1/PD-1 expression. Simultaneously, these EVs inhibited apoptosis in UBC cells, enhanced the invasion capability of T24 cells, and reduced the secretion of IFN-γ, IL-2, and TNF-α from CD8 + T cells, implying their potential role in inducing immunotherapy resistance of UBC [117].

Therapeutic potential of CAF-derived EVs

In the previous sections, we summarized the biological functions and detailed mechanisms of CAF-derived EVs in mediating cancer therapy resistance, providing evidence for the promising therapeutic potential of CAF-derived EVs in cancer management (Fig. 3). In this section, we will summarize and discuss the promising potential of CAF-derived EVs as clinical biomarkers and novel therapeutic targets for enhancing therapeutic efficacy.

CAF-derived EVs as clinical biomarkers

Cancer is a highly heterogeneous disease involving diverse components, hence, developing effective cancer biomarkers is a critical way to represent cancer status and monitor cancer progression [118]. Liquid biopsy is a novel approach that collects biofluid specimens and provides more opportunities for early cancer diagnosis, prognosis prediction, and treatment efficacy evaluation [118, 119]. The large amounts of circulating EVs in biofluids produced by different cell types have become a critical component in liquid biopsies. For instance, Hoshino et al. have conducted a large-scale and comprehensive proteomic analysis of exosomes and exomeres from 426 human samples to develop novel diagnostic biomarkers [120]. Nowadays, a large number of clinical trials have been conducted to evaluate the therapeutic potential of EVs as diagnostic and prognostic biomarkers

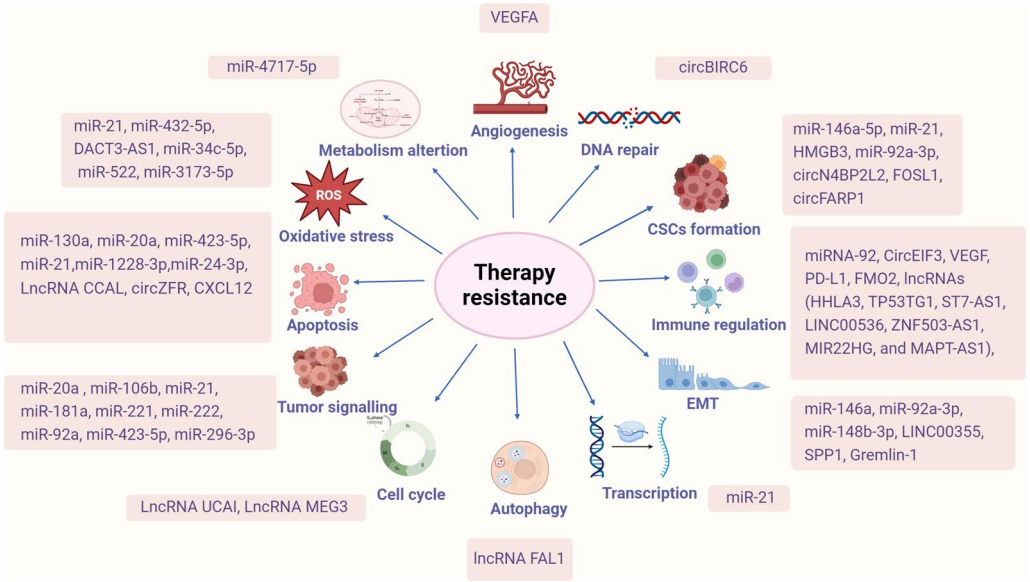


Fig. 3 CAF-derived EVs mediate cancer therapy resistance through complex mechanisms. CAF-derived EVs can deliver multiple cargoes to tumour cells, including miRNAs, lncRNAs, circRNAs and proteins. They can mediate the resistance to chemotherapy, targeted therapy, radiotherapy, and immunotherapy through multiple biological mechanisms, such as regulation of autophagy, EMT, and cancer stemness, metabolism, angiogenesis, DNA repair, immune infiltration, cell cycle, transcription and oncogenic signalling pathways

for diverse cancers. For instance, blood plasma samples from 420 lung cancer patients and 150 healthy controls were obtained to purify the exosomes in a recent clinical trial (ClinicalTrials.gov Identifier: NCT04529915). Deep-learning analysis of exosomes is performed to screen exosomal proteins for lung cancer early diagnosis and distinguish lung cancer patients in different clinical stages to improve the prognosis. In 2016, the first exosome-based liquid biopsy ExoDx™ Lung (ALK), was developed for the isolation and analysis of exosomal RNA from blood samples, which can effectively detect EML4-ALK mutations in NSCLC patients with 88% sensitivity and 100% specificity, thereby providing a more direct and sensitive approach to detect gene muutations than cfDNA [119]. The ExoDx Prostate IntelliScore (EPI), approved by the FDA, can effectively predict the risk of higher-grade prostate cancer for patients with PSA from 2 to 10 ng/mL by analyzing ERG, PCA3, and SPDEF RNA in exosomes [121]. Three independent, prospective, and multicenter clinical trials have reported that EPI can outperform the standard of care and serve as a novel biomarker for the early diagnosis of prostate cancer [122]. Another multicenter study has confirmed that GATA2 mRNA concentration in EVs in urine can effectively improve the detection of high-risk prostate cancer and may avoid unnecessary prostate biopsies [123]. In addition, MedOncAlyzer 170, a newly developed liquid biopsy system, has been developed for detecting exosomal RNA and ctDNA in a single trial. It can identify significant and functional mutations in multiple cancer types in a small volume (0.5 ml) of patient blood or plasma. Due to the unique way exosomes and ctDNA are formed, MedOncAlyzer 170 is accurate and highly sensitive to detect mutations at all stages of cancer progression and treatment [119].

Multiple experimental studies have evaluated the ectopic expression of diverse cargoes in CAF-derived EVs during cancer progression, and these cargoes are significantly correlated with clinical pathological features of cancer patients, thus highlighting the promising potential of CAF-derived EVs as biomarkers in the diagnosis and prognosis of various cancers. For instance, CAF-derived exosomal miR-196a is critically involved in HNC progression and chemoresistance, and plasma exosomal miR-196a levels were higher in HNC patients compared with healthy controls. Exosomal miR-196a levels were significantly higher in the plasma of patients with poor chemotherapeutic responses, larger tumor size, lymph node metastasis, and advanced tumor stage. Kaplan-Meier analysis and Cox proportional hazards regression analysis further confirmed that plasma exosomal miR-196a is a critical prognostic biomarker for HNC patients [124]. Similarly, miR-3188 is significantly downregulated in CAF-derived exosomes from HNC patients, and plasma miR-3188 levels were also downregulated in HNC patients and upregulated after tumour excision. A receiver operating characteristic (ROC) curve identified that plasma miR-3188 levels could serve as a diagnostic

biomarker for HNC patients and low plasma miR-3188 expression was significantly correlated with larger tumor sizes and advanced TNM stage [125]. In HCC, miR-150-3p was significantly downregulated in CAF-derived exosomes and patients with low miR-150-3p levels in plasma exosomes had a worse prognosis [126]. Notably, several ongoing studies have been conducted to evaluate the potential of EVs as predictive biomarkers for cancer therapeutic efficacy. For instance, a previous study based on 18 melanoma and 8 NSCLC patients under anti PD-1 therapy has revealed that downregulation of PD-L1 mRNA in EVs was detected in patients with partial or complete immunotherapy response compared with those with progressive disease [127]. A recent clinical trial is designed to evaluate the response to immunotherapy (pablolizumab and nafulizumab) by measuring the PD-L1 and miRNA expression in plasma exosomes in pre- and post-treated NSCLC patients and correlates it with the treatment outcome (NCT04427475). Another ongoing clinical trial in Limoges (NCT03985696) is conducted to explore the expression of therapeutic targets (as CD20, PDL-1) in exosomes and immunotherapy resistance in patients with aggressive Non-Hodgkin B-cell lymphomas (B-NHL). Despite most of the current clinical trials being in Phase 0 or the initiation of recruitment, we believe that EVs will become promising and reliable clinical biomarkers and will eventually go to the clinic. In summary, diverse CAF-derived exosomal cargoes in body fluids across pan-cancers may function as non-invasive biomarkers in liquid biopsy for early diagnosis and clinical prediction.

CAF-derived EVs as therapeutic targets

Multiple lines of evidence have demonstrated that CAF-derived EVs actively participate in cancer tumorigenesis and progression. Hence, targeting CAFs and CAF-derived EVs has opened new avenues for cancer treatment. For instance, CAFs can promote intrahepatic cholangiocarcinoma progression by delivering miR-493-5p in EVs, highlighting that inhibiting miR-493-5p in CAFs may be a novel therapeutic strategy for intrahepatic cholangiocarcinoma treatment [128]. The CXCR4 antagonist motixafortide (BL-8040) has been found to inhibit the immunosuppressive CXCL12-CXCR4 axis mediated by FAP + CAFs and has been applied in combination with pembrolizumab and/or chemotherapy for the treatment of pancreatic cancer patients in phase II clinical trial (NCT02826486). CAF-derived ANXA6 EVs carry the ANXA6/LRP1/TSP1 complex to facilitate pancreatic cancer aggressiveness and depletion of ANXA6 in CAFs impaired complex formation and inhibited pancreatic cancer metastasis occurrence [129]. Inhibiting the biosynthesis and secretion of tumour-promoting EVs and blocking the endocytosis of tumour-promoting EVs by cancer cells have been investigated in multiple cancers recently. Several agents, such as tipifarnib and manumycin A have been reported to selectively inhibit tumour cell-released exosomes but exert no effects on normal cells [130]. Xi et al. have found that can stimulate ATM activation and facilitate autophagy-associated exosome release from CAFs to induce breast cancer cell invasion, and inhibition of oxidized ATM kinase by KU60019 (a small-molecule inhibitor of activated ATM) or shRNA effectively inhibits the exosome secretion from hypoxia-induced CAFs, subsequently inhibiting breast cancer progression [24]. Hence, specific inhibition of tumour-promoting EVs from CAFs may provide a novel method to inhibit cancer progression and reverse therapy resistance. In addition, the loss of specific cargoes in CAF-derived EVs may also contribute to cancer initiation and progression. For instance, miR-3188 was abnormally downregulated in CAF-derived exosomes in HNC, and loss of CAF-derived exosomal miR-3188 resulted in HNC progression in vivo and in vitro. Besides, miR-3188-loaded exosomes significantly inhibited tumor growth in vivo [125]. Hence, delivering anti-tumour agents by EVs may effectively inhibit tumour growth and improve patient prognosis. Inspiringly, several EV-delivered vaccines have entered clinical trials. For example, an ongoing phase II clinical trial (NCT01159288) is conducted to evaluate the safety and efficacy of dendritic cell-derived exosomes loaded with tumor antigens in 41 participants. Another early phase I clinical trial (NCT05559177) is designed to explore the therapeutic efficacy of chimeric exosomal tumor vaccines for recurrent or metastatic bladder cancer.

Perspectives and challenges

Multiple lines of evidence have revealed that CAF-derived EVs are critically involved in cancer therapy resistance with promising clinical significance and therapeutic potential. Targeting specific therapy resistance-associated CAF-derived EVs is a promising approach for overcoming cancer therapy resistance. In addition, CAF-derived EVs can function as noninvasive biomarkers in liquid biopsy, and may effectively improve the prediction of cancer patients' therapeutic responses and prognosis [119]. Furthermore, engineered exosomes can function as a drug delivery system to deliver cargoes to specific cancer sites spatially and release the anti-cancer drugs temporally with enhanced efficacy and low side effects [131]. Recent studies have also illustrated that EVs may exert promising effects in repairing radiotherapy-related tissue damage by various mechanisms, such as promoting angiogenesis and inhibiting inflammation and fibrosis [132, 133]. Also, EVs have promising potential to treat

cancer-related cachexia, which is a major complication of human malignancies and seriously affects the quality of life and prognosis of cancer patients [134]. Although promising progress has been achieved in illustrating the biological roles of CAF-derived EVs, several important unanswered questions and limitations should be resolved before the clinical application of CAF-derived EVs in cancer management.

Firstly, the categorization and classification of CAF subgroups lack a unified, standardized framework to address the diverse findings reported by different research teams, often within the same cancer category and utilizing comparable scRNA-seq or CyTOF methodologies. The subdivision and characterization of CAF subgroups appear subjective, leading to potential variations among observers [16]. Consequently, reaching a consensus on key biomarkers and hierarchical clustering patterns defining CAF subgroups through scRNA-seq or CyTOF analyses is imperative for the forthcoming period. Currently, there are still several challenges in applying scRNA-seq to investigate CAFs heterogeneity. For example, CAFs are difficult to isolate, because they are embedded in the ECM. Hence, CAFs are often underrepresented in scRNA-seq investigation, and developing tissue-specific protocols for CAFs isolation is warranted [135]. Furthermore, the establishment of a standardized experimental platform featuring particular, specialized, and dependable tools and methodologies is essential for identifying, marking, segregating, cultivating, and functionally evaluating CAF subgroups both in artificial settings and within living organisms, akin to the protocols instituted for investigating immune cell populations. This standardization will facilitate the accurate delineation and description of CAF subgroups with designated functional roles and predictive significance, streamlining the design of tailored therapeutic strategies targeting specific CAF subpopulations or pathways in the future.

Secondly, the classifications for CAF-derived EVs remain elusive, with a recent study proposing isolation and characterization methods for six distinct EV subsets found in tissues. Despite these efforts, a universally accepted international categorization system for CAF-derived EVs is lacking, leaving doubts about the impact of inconsistent isolation and purification techniques on past findings. Future investigations ought to differentiate between various CAF-derived EV subsets and evaluate their anti-tumour potential. Additionally, the absence of systematic guidelines and procedures for the extraction, purification, and preservation of CAF-derived EVs poses a challenge to their clinical utilization. The employment of diverse isolation and purification approaches yields varying subpopulations of CAF-derived EVs possessing unique compositions, properties, and biological functions. Consequently, innovative standardized methodologies aligned with good manufacturing practices (GMP) are imperative for advancing CAF-derived EVs research.

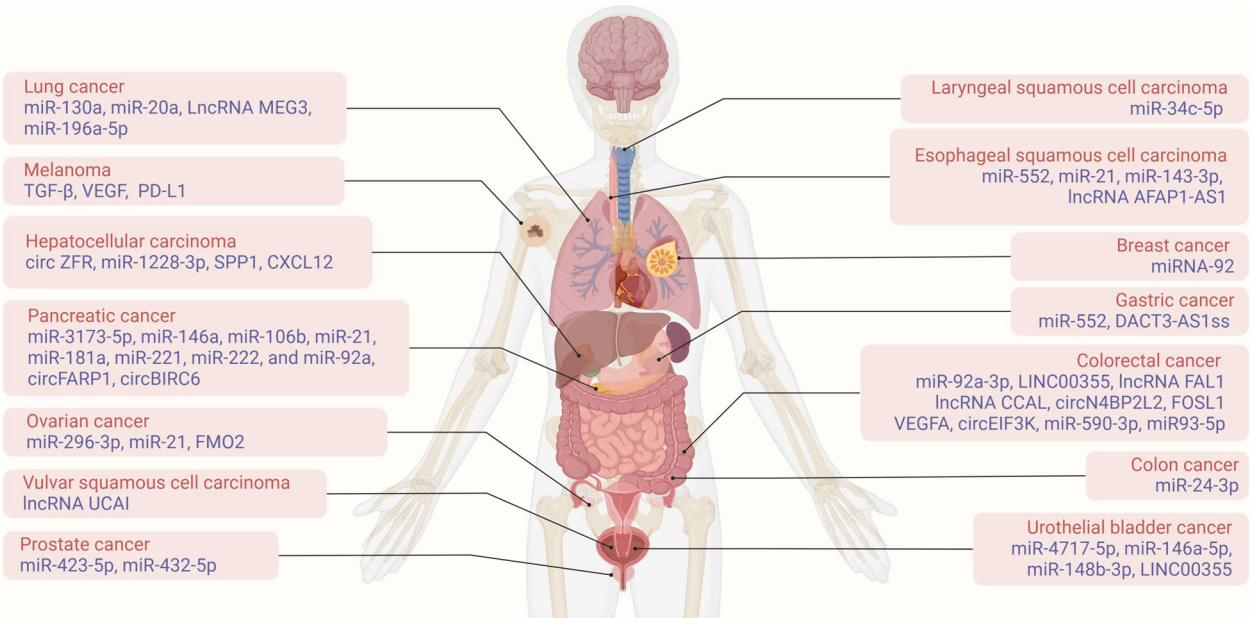


Fig. 4 Therapy resistance-related CAF-derived EVs in different cancers. CAF-derived EVs deliver miRNAs, lncRNAs, circRNAs and proteins to cancer cells, thus influence the therapy resistance of multiple cancer types, such as lung cancer, melanoma, and hepatocellular carcinoma. These cargoes in CAF-derived EVs may serve as novel therapeutic targets for reversing therapy resistance and clincal biomarkers for predicting therapy efficacy in cancer management

Lastly, inhibiting the biogenesis and secretion of tumour-promoting CAF-derived EVs presents an innovative avenue for inhibiting cancer progression and therapy resistance, necessitating a profound comprehension of the biogenesis and release mechanisms of EVs. For instance, the Tspan family plays critical roles in regulating EV biogenesis, function, and targets, and Tspan proteins can regulate multifaced cancer behaviours and serve as clinical biomarkers [136]. Hence, targeting Tspan proteins may open new avenues for regulating EV biogenesis and functions and inhibiting tumour growth in anticancer therapeutic strategies [136, 137]. Nowadays, several EVs inhibitors have been investigated in cancer treatment, such as imipramine and pantethine for inhibiting EVs production, and bisindolylmaleimide I and macitentan for inhibiting EVs release [138]. Employing targeted siRNA or CRISPR/Cas9-loaded EVs, alongside multitarget pharmacological approaches to inhibit EV activity, also represents a novel therapeutic option for targeted CAF-derived EVs therapy. Nevertheless, challenges such as off-target effects, secure delivery modalities, nonspecific inhibition of non-cancerous EVs, and the triggering of compensatory pathways in EV formation and release pose significant hurdles. Beyond therapeutic efficacy, the reproducibility and efficiency of primary compounds for halting EV production necessitate further evaluation, especially since certain approved therapeutics with EV-targeting capabilities have displayed adverse effects in humans. For instance, imipramine, a tricyclic antidepressant, can result in undesirable outcomes, such as immune suppression and infection due to its interference with EVs formation via acid sphingomyelinase inhibition [139].

Conclusions

In conclusion, we discussed and summarized recent discoveries and research progress on the biological mechanisms of CAF-derived EVs in mediating therapy resistance in various cancers (Fig. 4). We further emphasized the clinical significance and implications of CAF-derived EVs in cancer management, which provides a novel direction for reversing cancer therapy resistance and improving patient prognosis. Due to the key role of CAF-derived EVs in mediating cancer therapy resistance, further in-depth studies are needed to illustrate the detailed mechanisms of CAF-derived EVs in cancer therapy failure and develop novel CAF-derived EVs-targeted therapeutic strategies to overcome cancer therapy resistance in the clinic.

Abbreviations

ACT	Adoptive cell transfer
ALK	Anaplastic Lymphoma Kinase
APAF1	Apoptosis protease activating fator1
ATC	Anaplastic thyroid cancer
CAFs	Cancer-associated fibroblasts
CAR	Chimeric antigen receptor
cfDNA	Cell free DNA
circRNAs	Circular RNAs
CRC	Colorectal cancer
CSCs	Cancer stem cells
CTLA4	Cytotoxic T-lymphocyte associated protein 4
DDP	Cisplatin
DOX	Doxorubicin
DTX	Docetaxel
ECM	Extracellular matrix
EMT	Epithelial-mesenchymal transition
EOC	Epithelial ovarian cancer
EPI	ExoDx Prostate IntelliScore
ESCC	Esophageal squamous cell carcinoma
EVs	Extracellular vesicles
FGF5	Fibroblast growth factor 5
FMO2	Flavin containing monooxygenase 2
FOSL1	Recombinant FOS Like Antigen 1
GC	Gastric Cancer
GEM	Gemcitabine
GMP	Good manufacturing practices
HCC	Hepatocellular carcinoma
HGF	Hepatocyte growth factor
HNC	Head and Neck Cancer
HuR	Human antigen R
ICIs	Immune Checkpoint Inhibitors
ITGB4	Integrin β4
LncRNAs	Long non-coding RNAs
LSCC	Laryngeal squamous cell carcinoma
MIF	Migration inhibitory factor
miRNAs	MicroRNAs
M-MDSCs	Monocytic myeloid-derived suppressor cells
MTX	Methotrexate
ncRNAs	Non-coding RNAs
NFs	Normal Fibroblasts
NHEJ	Non-homologous end joining
NSCLC	Non-small cell lung cancer
OXA	Oxaliplatin
PDAC	Pancreatic Ductal Adenocarcinoma
PIAT	PNI-associated transcript
PTX	paclitaxel
SCC	squamous cell carcinoma
SCLC	small cell lung cancer
shRNA	short hairpin RNA
SNAIL	Snail zinc finger transcription factor
SPP1	secreted phosphoprotein 1
SUMO1	Small Ubiquitin Like Modifier 1
TKIs	Tyrosine Kinase Inhibitors
TP53INP1	Tumor protein p53-inducible nuclear protein 1
UBC	urothelial bladder cancer
VEGFA	Vascular Endothelial Growth Factor A
YBX1	Recombinant Y-Box Binding Protein 1

Acknowledgements

Not applicable.

Authors' contributions

ZJL, and TL contributed to conceive, design and revision of the manuscript sections. ZJL, and GQL wrote the manuscript. KJ and GQL designed figures and created Tables. TL and ZH L supervised the manuscript by providing critical feedbacks and revisions. The authors read and approved the final manuscript.

Funding

This study was supported by grants from National Natural Science Foundation of China (NO. 81871783 and 82072441), Hunan Outstanding Youth Fund Project Grant (NO. 2022JJ10095).

Availability of data and materials
Not applicable.

Data availability
Not Applicable.

Declarations

Ethics approval and consent to participate
No datasets were generated or analysed during the current study.

Consent for publication
All authors consent to publication.

Competing interests
The authors declare no competing interests.

Received: 31 July 2024 Accepted: 2 September 2024
Published online: 07 September 2024

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