Cancer-associated fibroblast-derived extracellular vesicles in the tumor microenvironment and their medical importance (Review)

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Abstract. Cancer is a heterogeneous group of diseases that can originate in any tissue or organ of the body, which is characterized by the uncontrollable proliferation of abnormal cells and, in some cases, the invasion of nearby tissues or other parts of the body. In recent decades, research has expanded beyond cancer cells, considering the complex interactions within the surrounding tissues due to the heterogeneous nature of cancer. Notably, cancer cells release extracellular vesicles (EVs) into the tumor microenvironment (TME), which influence stromal cells; specifically, they induce the reprogramming of fibroblasts into the cancer-associated fibroblast (CAF) phenotype, making these cells important targets of EV-mediated cross-talk. Accordingly, CAFs serve a key role in tumorigenesis, angiogenesis, tumor development, metastasis and drug resistance by secreting various pro-oncogenic factors. In addition, CAFs can secrete EVs, which further contribute to these processes. These EVs function as a unique form of intercellular communication that can promote cell proliferation and survival, help shape the TME, and increase invasive and metastatic activity. The present review was prompted by the growing recognition of the crucial yet still incompletely understood role of CAF-derived EVs from the TME in driving tumorigenesis, growth and metastasis, highlighting the need for further exploration.

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Abbreviations: CAF, cancer-associated fibroblast; EV, extracellular vesicle; TME, tumor microenvironment; EMT, epithelial-mesenchymal transition; miRNA, microRNA; lncRNA, long non-coding RNA; PD-L1, programmed death-ligand 1; ECM, extracellular matrix; COL1A1, collagen type I α1; MMP-1, matrix metalloproteinase-1

Key words: cancer, tumor microenvironment, extracellular vesicle, cancer-associated fibroblast, stroma, fibroblasts, cancer-associated fibroblast phenotype, cancer therapy

Contents

1. Introduction

Cancer comprises a group of diseases characterized by uncontrolled growth and dissemination of genetically altered cells. These cells, following genetic mutations or alterations, proliferate abnormally, and can invade adjacent tissues or metastasize to distant sites through the blood and lymphatic systems (1). Notably, cancer is the second leading cause of death worldwide (2). According to GLOBOCAN 2022 and the International Agency for Research on Cancer, there were 20 million new cancer cases and 9.7 million cancer-related deaths globally in 2022 (3). Furthermore, the global cancer burden is projected to increase to 28.4 million cases by 2040, representing a 47% rise from 2020 (3,4).

The rising global cancer burden has enhanced awareness of its impact and increased the demand for effective scientific solutions. This trend has accelerated cancer research in recent decades, particularly in cancer biology and the role of the tumor microenvironment (TME) in cancer progression (5-7). The TME is a complex ecosystem of cellular and non-cellular components that surrounds tumors, and consists of both

non-cancerous and cancerous cells (8-11). Ample evidence has indicated that the TME facilitates the acquisition and maintenance of cancer hallmarks, such as sustained proliferative signaling, resistance to cell death, angiogenesis, invasion and metastasis, tumor-promoting inflammation and immune evasion (7,12-14) (Fig. 1).

Over the past two decades, research has increasingly focused on the interactions between cancer cells and the TME, where the TME serves as the 'soil' supporting the proliferation of tumor cell 'seeds' (9,15-18). Studies have demonstrated that tumor growth is influenced not only by malignant cancer cells themselves, but also by the surrounding components of the tumor stroma, which serve essential roles in facilitating early tumorigenesis following oncogenic transformation by supporting the survival and expansion of genetically altered cells, as well as promoting tumor progression and metastasis (17,19-21). During early tumor development, a dynamic and reciprocal relationship forms between cancer cells and TME components, supporting cancer cell survival, local invasion and metastatic dissemination (22). The stromal cells within the TME include mesenchymal stromal cells, pericytes, fibroblasts and cancer-associated fibroblasts (CAFs).

CAFs maintain tumor characteristics by secreting soluble paracrine signals and releasing extracellular vesicles (EVs), which serve as the instrument of intercellular communication in the TME and contribute to numerous processes associated with tumor progression, including proliferation, angiogenesis and metastasis (23-25). Therefore, the present review was prompted by the increasingly evident yet still incompletely understood role of CAF-derived EVs from the TME in tumorigenesis, growth and metastasis. Gaining deeper insights into these mechanisms could result in the identification of innovative therapeutic strategies, ultimately transforming cancer treatment and improving outcomes for patients worldwide.

2. CAFs

Fibroblasts, which constitute the major component of the stroma, were first described in the late 19th century based on their anatomical location and microscopic appearance (17,20,26). These cells are the most abundant residents of connective tissue, primarily responsible for synthesizing and maintaining extracellular matrix (ECM) components, such as collagen, laminin, fibronectin and proteoglycans. By contrast, CAFs are a subset of fibroblasts that become activated within the TME (27); CAFs differ from normal fibroblasts by exhibiting notable heterogeneity and plasticity, and they serve a pivotal role in cancer progression and development (19).

CAFs constitute the most abundant cellular component of the tumor stroma and influence multiple tumor processes, including the induction of tumor cell proliferation (28), modulation of tumor angiogenesis (29), establishment of an immunosuppressive microenvironment that enables immune evasion (30), and promotion of tumor formation and drug resistance (31). They can originate from both resident cells within the TME [such as fibroblasts, epithelial cells via epithelial-to-mesenchymal transition (EMT), endothelial cells via endothelial-mesenchymal transition, pericytes and adipocytes through transdifferentiation] and from distant sources, including bone marrow-derived mesenchymal stem cells (32). In addition to fibroblasts, other stromal cells, such as mesenchymal stem cells and adipocytes, can be activated by TGF-β and platelet-derived growth factors (PDGFs) to acquire a CAF phenotype (17,27,33). However, the precise origins of CAFs, their specific niches within various tumor types, and their functional roles remain incompletely understood (34). The heterogeneity of CAFs may be related to the diversity of cellular origin, phenotype and function. Irrespective of origin, the transition of cells to CAFs is largely irreversible, and yet remains plastic with respect to the CAF phenotype within or across tumor types (34). Despite advances in the field, unresolved questions and controversies persist in CAF research. For example, the mechanisms underlying CAF differentiation, and the specific roles of CAFs in tumor metastasis and drug resistance are still being debated. Furthermore, the potential for therapeutic targeting of CAFs to improve cancer treatment outcomes remains controversial. These knowledge gaps underscore the complexity of CAF biology and represent critical frontiers in cancer research.

CAFs contribute to tumorigenesis, angiogenesis, tumor progression, metastasis and therapeutic resistance by secreting pro-oncogenic factors, ECM components, cytokines and EVs. These secretions modulate tumor angiogenesis, reprogram tumor metabolism, regulate immune responses within the TME and remodel the ECM (35,36). CAFs represent the most abundant stromal cell population in the TME and are a critical component of the tumor mesenchyme, where they serve an important role in promoting tumor malignancy (7). They modulate the biological functions of tumor cells via multiple methods, including the secretion of a number of bioactive molecules that influence paracrine and autocrine signaling, the release of exosomes and direct interactions, thus affecting cancer initiation and development (24,37,38). Molecular markers for positive CAF characterization are fibroblast activation protein (FAP), fibroblast-specific protein 1 (FSP1), PDGF receptors (PDGFRs), podoplanin, α-smooth muscle actin (α-SMA) and vimentin, whereas CD31 and cytokeratin are used for negative CAF characterization (32,39-41). Multiple studies have demonstrated that cooperative signaling loops between cancer cells and surrounding CAFs can influence therapeutic response and cancer prognosis, highlighting the predictive and prognostic importance of CAFs and their secreted factors (42-44).

Different CAF subtypes have been identified with specific molecular markers, such as myofibroblast-like CAFs (myCAFs) (45), inflammatory CAFs (iCAFs) (45) and antigen-presenting CAFs (ApCAFs) (34,46), which perform different and, in some cases, even contradictory roles in tumorigenesis. Across cancer types, myCAFs are associated with high ECM production, which can facilitate tumor progression by creating a supportive stroma for cancer cells to thrive. By contrast, non-myofibroblastic iCAFs are generally characterized by inflammatory secretions that contribute to a pro-tumorigenic environment through the secretion of cytokines that promote cancer cell survival and proliferation (34). Furthermore, ApCAFs have been implicated in modulating immune responses within the TME, potentially affecting tumor growth dynamics. Studies in genetically engineered mouse models and clinical studies have suggested that there may exist at least two functionally different populations of CAFs:

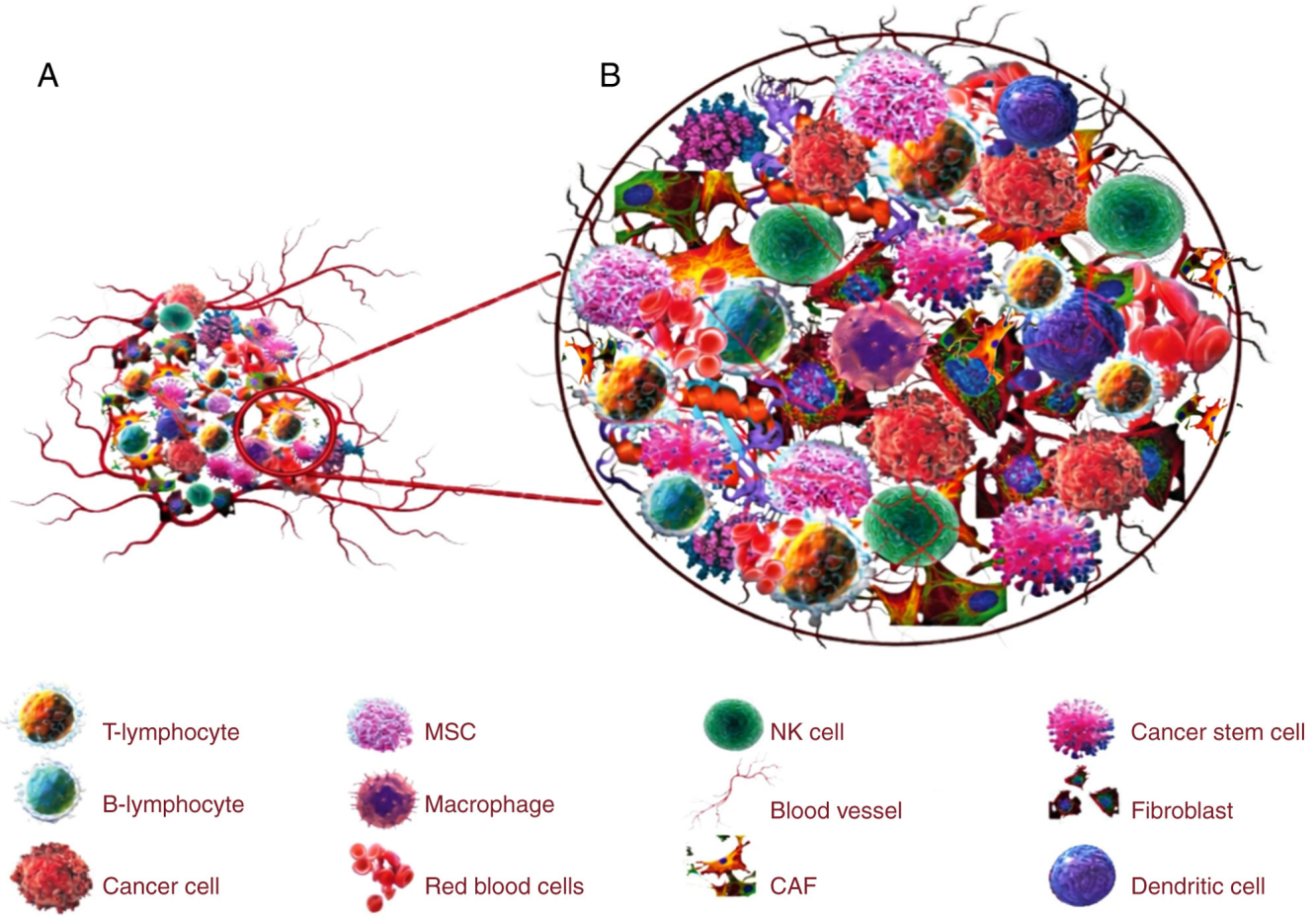

Figure 1. Overview of the TME. (A) A tumor mass within its surrounding microenvironment. (B) A magnified view of the TME, highlighting the diverse cellular components and structural elements present. These include malignant cancer cells; stromal cells such as MSCs, fibroblasts and CAFs; immune cells including T-lymphocytes, B-lymphocytes, macrophages, dendritic cells and NK cells; as well as red blood cells and blood vessels. These components form a dynamic and interactive microenvironment that supports tumor progression and cellular cross-talk. CAF, cancer-associated fibroblast; MSC, mesenchymal stromal cell; NK, natural killer; TME, tumor microenvironment.

Cancer-promoting CAFs (pCAFs) and cancer-restraining CAFs (rCAF) (45,47,48). Although various pCAF markers have been identified (for example, α-SMA, FAP and FSP1), the identity of rCAFs remains unknown, probably due to the lack of rCAF-specific markers (19,48,49). Understanding these functional implications is crucial for developing targeted therapies that can inhibit pCAFs while preserving or enhancing the activity of rCAFs.

3. EVs

EVs are phospholipid bilayer membrane-enclosed vesicles secreted by all cell types (11). Depending on their cellular origin, EVs contain a diverse range of cargo, including membrane, cytosolic and nuclear proteins, as well as noncoding RNAs, other RNA types and double-stranded DNA fragments. Notably, >50 years ago, researchers observed the release of tiny sacs from cultured cells, although their importance was initially unclear (50). These structures, later termed EVs, revealed a previously unrecognized network of intercellular exchange. It is now established that all cells release EVs as part of normal physiological processes and these roles are often co-opted during disease states, particularly in cancer progression (51). The discovery of EVs has generated notable scientific interest, leading to a field of research that has reshaped the understanding of cell communication, and holds considerable promise for disease diagnostics and therapeutics.

Currently, EVs encompass a wide range of specialized particles, including exosomes, other small exosome-sized EVs, microvesicles (MVs), arrestin domain-containing protein 1-mediated MVs (ARMMs), apoptotic bodies and large oncosomes (52-54). For clarity, EVs are classified based on size and intracellular origin or biogenesis, as these criteria provide clear and consistent differentiation among EV types. Accordingly, two major classes of EVs are recognized: MVs and exosomes (53,55-58) (Fig. 2).

Exosomes typically range between 30 and 150 nm in diameter, and are formed by inward budding of late endosomal membranes that mature into multivesicular bodies (MVBs). Within the MVB, intraluminal vesicles (ILVs) are generated through inward budding of the limiting membrane. MVBs may be transported to the lysosome for degradation or directed to the plasma membrane for docking and fusion (53,59). Upon fusion with the plasma membrane, ILVs are released into the extracellular space as exosomes (60). Exosomes contain various surface proteins, including integrins, tetraspanins,

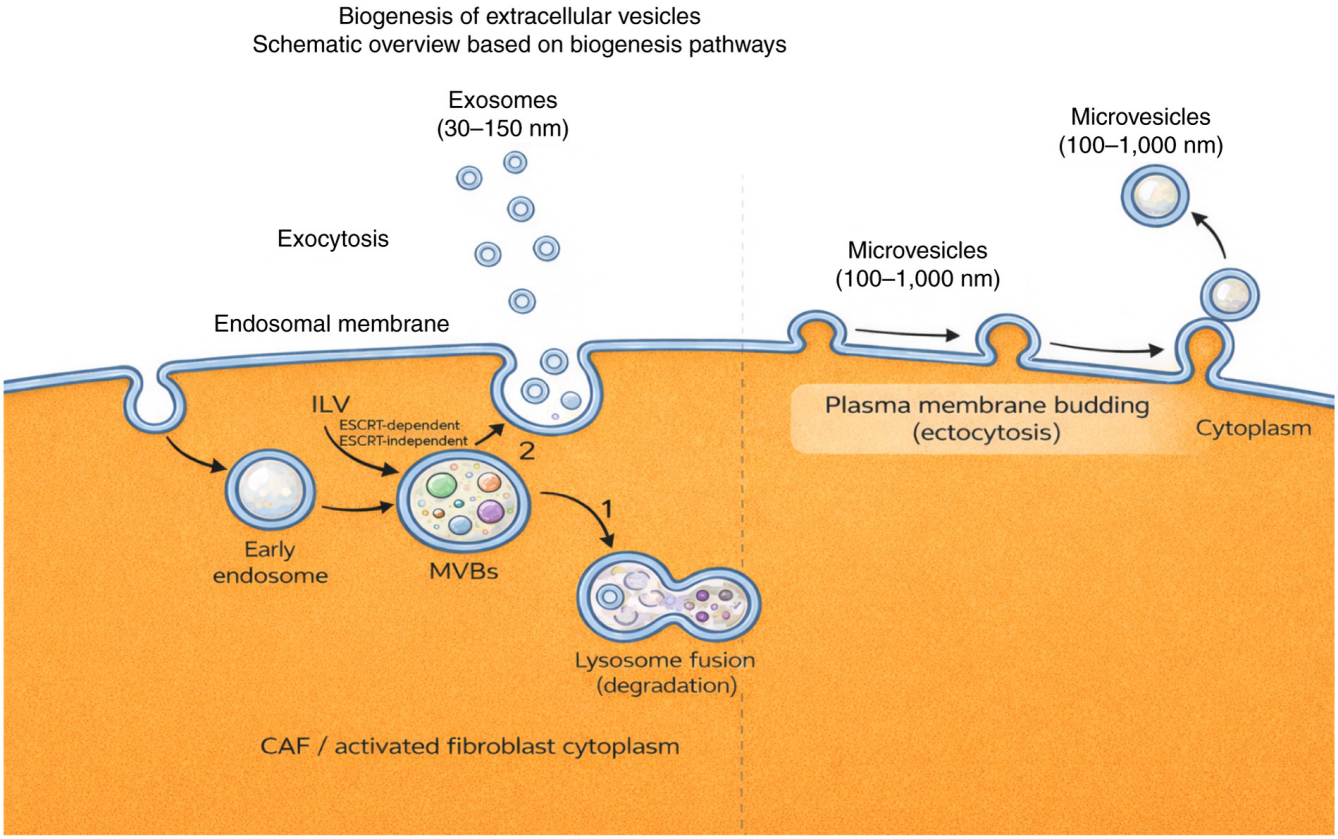

Figure 2. Biogenesis of EVs in activated fibroblasts/CAFs. Exosomes (30-150 nm) originate from the endosomal pathway through inward budding of the endosomal membrane, leading to the formation of ILVs within MVBs. ILV formation occurs via ESCRT-dependent and ESCRT-independent mechanisms, and enables selective cargo sorting, including proteins, lipids and nucleic acids. MVBs may fuse with lysosomes for degradation (1) or with the plasma membrane to release ILVs as exosomes into the extracellular space (2). By contrast, microvesicles (100-1,000 nm) are generated by direct outward budding (ectocytosis) of the plasma membrane. These EV biogenesis pathways in CAFs contribute to intercellular communication within the tumor microenvironment. CAF, cancer-associated fibroblast; ESCRT, endosomal sorting complexes required for transport; EV, extracellular vesicle; ILV, intraluminal vesicle; MVB, multivesicular body.

immunomodulatory proteins and programmed death-ligand 1 (PD-L1). They also carry intracellular proteins, RNA, DNA, amino acids and metabolites. MVs (also known as ectosomes or microparticles), which include oncosomes, migrasomes and ARMMs (53,61), are larger vesicles ranging between 100 and 1,000 nm in diameter. These are assembled at and released from the plasma membrane through outward protrusion or budding (62,63). The MV membrane primarily consists of membrane lipids and proteins (62). Similar to exosomes, MVs contain a diverse array of cargo, including lipids, transmembrane and globular proteins, DNA, mRNA and microRNA (miRNA/miR) (62,63).

EVs act at both local and distant sites, and circulate in various biological fluids, such as blood, urine, bile, nasal secretions and saliva (11,64). They transfer their cargoes, which include DNA, various types of RNA, metabolites, lipids, signaling molecules and cell-surface receptors, between cells (Fig. 3), both in the direct vicinity of the source cells and at distant sites in the body following transmission in biological fluids (65,66). The legion of bioactive EV cargoes delivered to stromal cells results in a biological response in the recipient cells. Three mechanisms have been proposed for the interaction of EVs with target cells: i) EVs fuse with target cells and transfer their cargos into the cells; ii) EVs endocytose near target cells and release their cargos into the cells; and iii) receptor-ligand interactions activate signal transduction pathways (67).

Cancer cell-derived EVs function as a unique form of intercellular communication, which can promote cell proliferation and survival, help shape the TME, and increase invasive and metastatic activity. When the transfer of EV cargoes is from a cancerous cell within the TME to a non-cancerous cell within or outside the TME, it promotes different aspects of cancer progression. The response helps tumor cells to evade antitumor immunity, modify the TME and create an environment that is conducive for tumor growth. Briefly, EVs serve essential roles in the cross-talk between malignant tumor cells and resident cells of the TME (68), and malignant cell-derived EVs can influence the activation of stromal cells into CAFs.

4. EVs derived from cancer and CAFs

This section provides a cross-tumor summary of experimental evidence describing bidirectional EV-mediated communication between cancer cells and CAFs, highlighting conserved mechanisms observed across multiple solid tumor types.

EVs are emerging as master couriers that reprogram the stroma, serving a pivotal role in cancer progression and CAF induction. Damaged and diseased cells, including cancer cells, have been shown to shed higher amounts of EVs compared

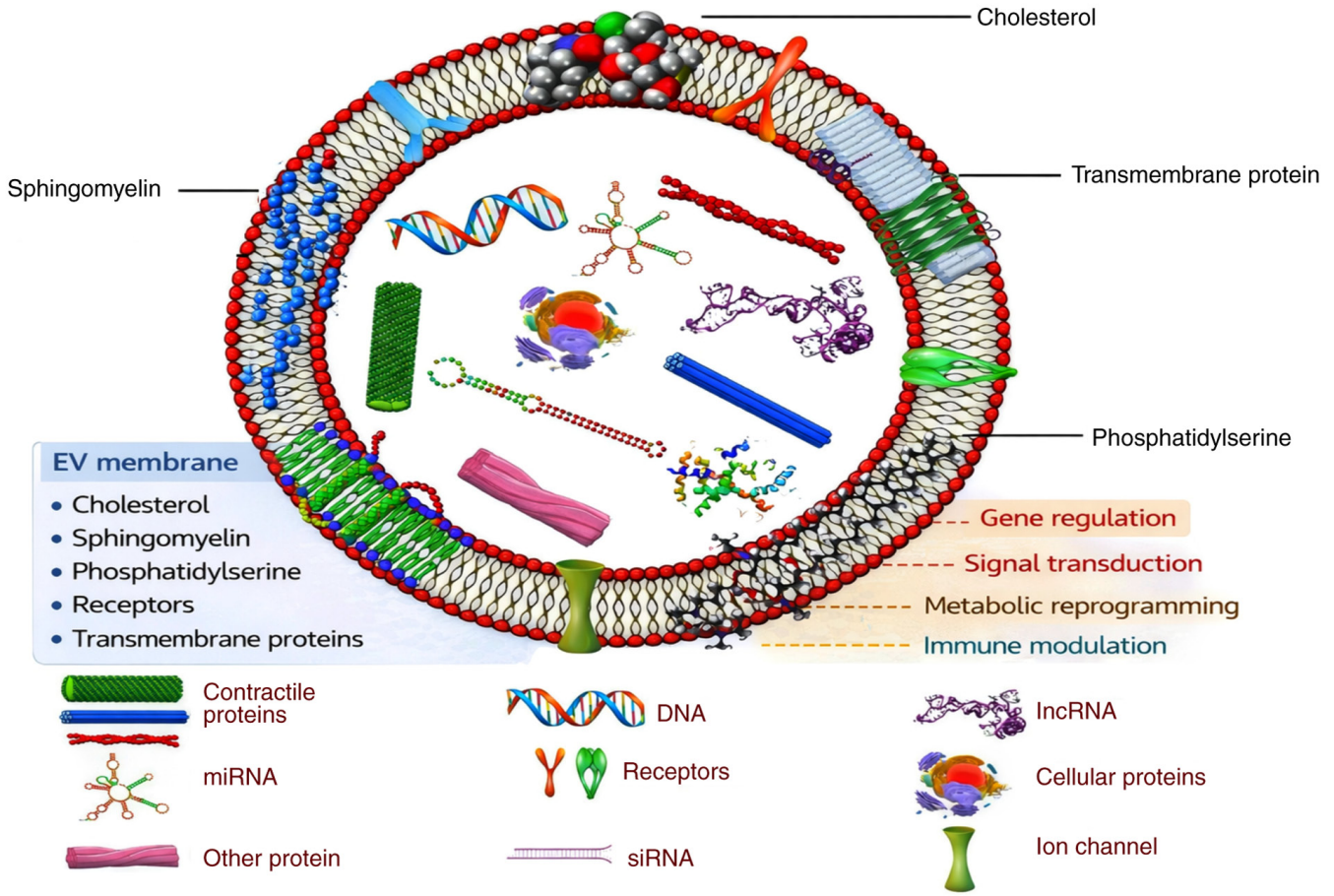

Figure 3. Structural and molecular composition of EVs. EVs are enclosed by a lipid bilayer enriched in cholesterol, sphingomyelin and phosphatidylserine, and display transmembrane proteins and surface receptors that mediate cellular recognition and uptake. The EV lumen contains diverse bioactive cargo, including nucleic acids (DNA, miRNAs, siRNAs and lncRNAs), cytoskeletal and contractile proteins, and other functional proteins. Together, these components enable EVs to participate in intercellular communication by regulating gene expression, signal transduction, metabolic reprogramming and immune modulation within the tumor microenvironment. EV, extracellular vesicle; lncRNA, long non-coding RNA; miRNA, microRNA; siRNA, small interfering RNA.

with their healthy counterparts (11). Al-Nedawi *et al* (69) discovered that highly aggressive forms of brain tumor cells produce large quantities of EVs. The EVs produced, when isolated and used to treat other brain cancer cells, have been shown to result in the recipient cells becoming more aggressive and growing faster, compared with untreated control cells (69,70). Mechanistically, EVs alter recipient cell behavior by transferring bioactive molecules, such as proteins, lipids and RNAs, which modulate signaling pathways involved in cell proliferation, migration and survival.

Tumors generally devise mechanisms for immune evasion in order to survive; such mechanisms include secretion of tumor immunomodulatory proteins, reduced expression of antigen-presenting proteins and EV secretion (71-73). EVs released from cancer cells have been reported to influence the immune system by interacting with T cells, natural killer cells and macrophages (18,74). Exosomes secreted by cancer cells can mediate immune evasion by downregulation of natural killer group 2 member D receptor expression in the effector cells (75).

Cancer cells have been reported to release EVs into the TME, which influence stromal cells, particularly via the reprogramming of fibroblasts into the CAF phenotype, to take up large numbers of cancer cell-derived EVs making them important targets of EV-mediated cross-talk (68,76). First, cancer cells release EVs containing various biomolecules into the surrounding tissue; subsequently, fibroblasts in the TME uptake these EVs, which promote changes in their phenotype. Studies have demonstrated that EVs derived from cancer cells induce the acquisition of a CAF-like phenotype in normal fibroblasts (18,77-79). Finally, these fibroblasts exhibit signature activation markers indicative of their new CAF phenotype (80). Furthermore, endothelial cells, pericytes and mesenchymal stem cells can be induced to a CAF phenotype by cancer-derived EVs (81-86). Cancer cell-derived EV cargoes also influence a pro-angiogenic or pro-inflammatory phenotype in CAFs, and the induction of therapy resistance and pre-metastatic niche formation (87).

Furthermore, CAFs can secrete their own unique EVs, which in turn get trafficked to cancer cells, where the cargoes are released to influence increased EMT, proliferation, invasion, metastasis, motility, stemness, colony formation, apoptosis inhibition, glycolysis and therapy resistance in these cancer cells (88). A unifying mechanism in this process is the alteration of signaling pathways such as the PI3K/AKT and Wnt/β-catenin pathways, which are heavily influenced by miRNA cargoes. The ability of cancer-derived EVs to promote CAF phenotype programming, and CAFs to secrete

EVs into adjacent tumor cells to modulate their behavior have been linked to several types of molecular cargo, including miRNAs, proteins and, to a lesser extent, mRNAs and long non-coding RNAs (lncRNAs) (89). Table I summarizes the key EV-associated miRNAs, mRNAs, lncRNAs and circular (circ)RNAs discussed in this section, including their cellular origin, target genes and functional outcomes across different tumor types (Fig. 4).

CAFs are also actively involved in remodeling the ECM, a process critical for tumor expansion by altering ECM stiffness and promoting its degradation, thus creating a microenvironment favorable to tumor progression (90). In triple-negative breast cancer, EVs released from MDA-MB-231 cells have been found to carry miR-9, which drives the transformation of normal fibroblasts into CAFs. This miRNA also modulates the expression of ECM-related genes, such as EGF-containing fibulin-like ECM protein 1, collagen type I α1 and matrix metalloproteinase 1 (71,91). However, it is essential to note that while these studies highlight notable interactions, they often work within controlled environments that may not entirely replicate the complex TME *in vivo*.

Evidence has demonstrated that CAF-derived EVs are not just passive byproducts of the tumor stroma, but active messengers capable of reprogramming cancer cell behavior particularly through the regulation of EMT. Across multiple tumor types, this regulation appears to occur through the selective delivery of miRNAs influencing signaling pathways such as PI3K/AKT and Wnt/β-catenin. In breast cancer, CAF-derived exosomal miR-21 promotes EMT and invasiveness by suppressing PTEN and activating PI3K/AKT signaling (92). Conversely, the delivery of miR-1-3p via CAF-derived EVs has been shown to suppress breast cancer progression and metastasis by inhibiting the GLIS1 pathway (84). In colorectal cancer, miR-92a-3p within CAF-derived EVs drives both EMT and stem-like properties by targeting FBXW7 and upregulating Wnt/β-catenin signaling (93). In prostate cancer, EVs enriched with miR-409 silence key tumor suppressors such as Ras suppressor protein 1 and STAG2, tilting the balance toward EMT and progression (94). These studies indicate that while the exact cargo and targets may differ, the capacity of CAF-derived EVs to steer EMT is a shared feature that is contextual, yet markedly consistent in function.

miRNAs are short non-coding RNA molecules, 18-22 nucleotides in length, which represent some of the most abundant components within EVs. These miRNAs serve a central role in modulating gene expression at the post-transcriptional level (95). They primarily bind to the 3' untranslated regions of target mRNAs, resulting in mRNA degradation or translational repression. Several studies have demonstrated that EV-associated miRNAs can induce a CAF phenotype in recipient cells by downregulating tumor suppressor genes, including p53 and related regulatory proteins (79,96,97). This effect is mediated through direct interactions with mRNA sequences encoding these tumor suppressors. For example, miR-21-enriched EVs, upon internalization by fibroblasts, activate PI3K signaling and promote their conversion into CAFs (24,86). Additionally, mRNAs for inflammatory cytokines such as TNF-α, TGF-β and IL-6 can be transferred from cancer cells to fibroblasts, influencing fibroblast function and differentiation (98). These cytokines initiate signaling cascades that activate transcription factors associated with inflammation and fibrosis. In melanoma, EVs have been shown to carry the lncRNA Gm26809, which upregulates CAF markers in recipient cells and further supports the pro-tumorigenic reprogramming of the tumor stroma (99). The lncRNA Gm26809 likely modulates chromatin remodeling or interacts with transcriptional machinery to regulate gene expression related to CAF activation.

CAFs also release EVs that facilitate metabolic reprogramming within the tumor ecosystem (81). However, it is important to acknowledge that EV populations are highly heterogeneous, and the specific cargo they carry can vary depending on the context and cellular origin. One notable mechanism involves CAFs expressing miR-105, which has been shown to contribute to metabolic adaptation. This adaptation occurs through the detoxification of lactic acid and ammonium, converting these byproducts into energy-rich metabolites to support cancer cell survival and proliferation (86). These CAFs are emerging as quiet but powerful players in shaping tumor metabolism. Within the often harsh and nutrient-limited environment of solid tumors, CAF-derived EVs enable cancer cells to adapt by supplying them with essential tools for survival. For example, in pancreatic ductal adenocarcinoma, CAF-EVs transfer tricarboxylic acid cycle metabolites and miR-106b, sustaining oxidative phosphorylation, enhancing metabolic plasticity and promoting tumor progression (100). Similarly, in breast cancer, CAF-derived EVs serve a crucial role in metabolic coupling, delivering key metabolites and supporting lactate recycling. This process ultimately fuels anabolic pathways and sustains tumor proliferation (71,101). These examples suggest that CAF-derived EVs do not merely instruct tumor cells but collaborate with them, creating a form of metabolic symbiosis that favors tumor growth even under stress.

Treatment of cultures of $CD8^+$ T cells with PD-L1, an exosome protein, has been shown to induce strong suppression of their growth and immune activity (102-104). Crucially, CAFs have been identified as a notable source of these PD-L1-carrying EVs in the TME. Studies in bladder and lung cancer have demonstrated that CAF-derived EVs either directly deliver PD-L1 to T cells or transfer genetic cargo that upregulates PD-L1 expression in neighboring tumor cells, thereby driving immune escape and $CD8^+$ T-cell exhaustion (105,106).

EV protein cargo frequently overlaps functionally with EV-associated miRNAs. TGF-β protein, miR-21, miR-769-3p and TGF-β mRNA have been implicated in driving CAF transformation in target cells, primarily through TGF-β signaling pathways (79,98,102,107-112). These signaling pathways, especially TGF-β, activate Smad proteins and promote transcriptional changes that enable cellular transformation and the acquisition of resistance characteristics. Moreover, CAF-derived EVs comprise active agents of therapy resistance, creating a notable impact on the tumor-stroma interplay. These vesicles do more than serve as passive byproducts of the tumor stroma; they actively facilitate immune evasion by delivering immunosuppressive cargo, including TGF-β-related proteins and regulatory miRNAs, which suppress cytotoxic T-cell activity (113). In multiple types of cancer, CAF-derived EVs contribute to therapy resistance by transferring miRNAs and other cargo that modulate apoptotic and survival pathways. For example, miRNAs such as miR-92a-3p delivered

Table I. Summary of EV-associated molecular cargoes including miRNAs, lncRNAs, mRNAs and circRNAs: Their cellular origin, target pathways and functional outcomes in the TME.

RNA cargo	EV source	CAF subtype	Recipient cell	Tumor type	Target gene/pathway	Functional outcome
miR-21	CAF-derived	Not specified	Cancer cells	Breast cancer	PTEN and PI3K/AKT	EMT and invasiveness
miR-92a-3p	CAF-derived	Not specified	Cancer cells	Colorectal cancer	FBXW7 and Wnt/β-catenin	EMT, stemness, invasion
miR-409	CAF-derived	Not specified	Cancer cells	Prostate cancer	RSU1, STAG2	EMT, tumor progression
miR-105	CAF-derived	Not specified	Cancer cells	Solid tumors	Metabolic genes (lactate/ammonia metabolism)	Metabolic reprogramming, tumor survival
miR-1-3p	CAF-derived	Not specified	Cancer cells	Breast cancer	GLIS1	Suppression of metastasis and progression
miR-106b	CAF-derived	Not specified	Cancer cells	Pancreatic cancer	Oxidative phosphorylation	Metabolic plasticity/progression
miR-9	Tumor cell-derived	Not applicable	Fibroblasts	TN breast cancer	EFEMP1, COL1A1, MMP-1	CAF conversion, ECM remodeling
miR-522	CAF-derived	Not specified	Cancer cells	Gastric cancer	Ferroptosis inhibition	Reduced chemosensitivity
miR-769-3p	Cancer cell-derived	Not applicable	Fibroblasts	Solid tumors	TGF-β signaling	CAF differentiation
circ_0067557	CAF-derived	Not specified	Cancer cells	Colorectal cancer	Lin28A and Lin28B	Malignant phenotypes
lncRNA Gm26809	Cancer-derived	Not applicable	Fibroblasts	Melanoma	CAF activation markers	Pro-tumorigenic reprogramming
lncRNA PWAR6	CAF-derived	myCAF	Cancer cells	Not specified	Not specified	Stemness and migration
mRNAs (TNF-α, TGF-β, IL-6)	Cancer-derived	Not applicable	Fibroblasts	Not specified	Inflammatory cascades	Fibroblast differentiation

Where the original studies did not explicitly distinguish between inflammatory CAFs and myofibroblast-like CAFs, the CAF subtype is indicated as 'Not specified'. CAF, cancer-associated fibroblast; circRNA, circular RNA; COL1A1, collagen type I α1; ECM, extracellular matrix; EFEMP1, EGF-containing fibulin-like ECM protein 1; EMT, epithelial-mesenchymal transition; EV, extracellular vesicle; lncRNA, long non-coding RNA; miRNA/miR, microRNA; MMP-1, matrix metalloproteinase 1; RSU1, Ras suppressor protein 1; myCAF, myofibroblast-like CAF; TN, triple negative; GLIS1, GLIS family zinc finger 1

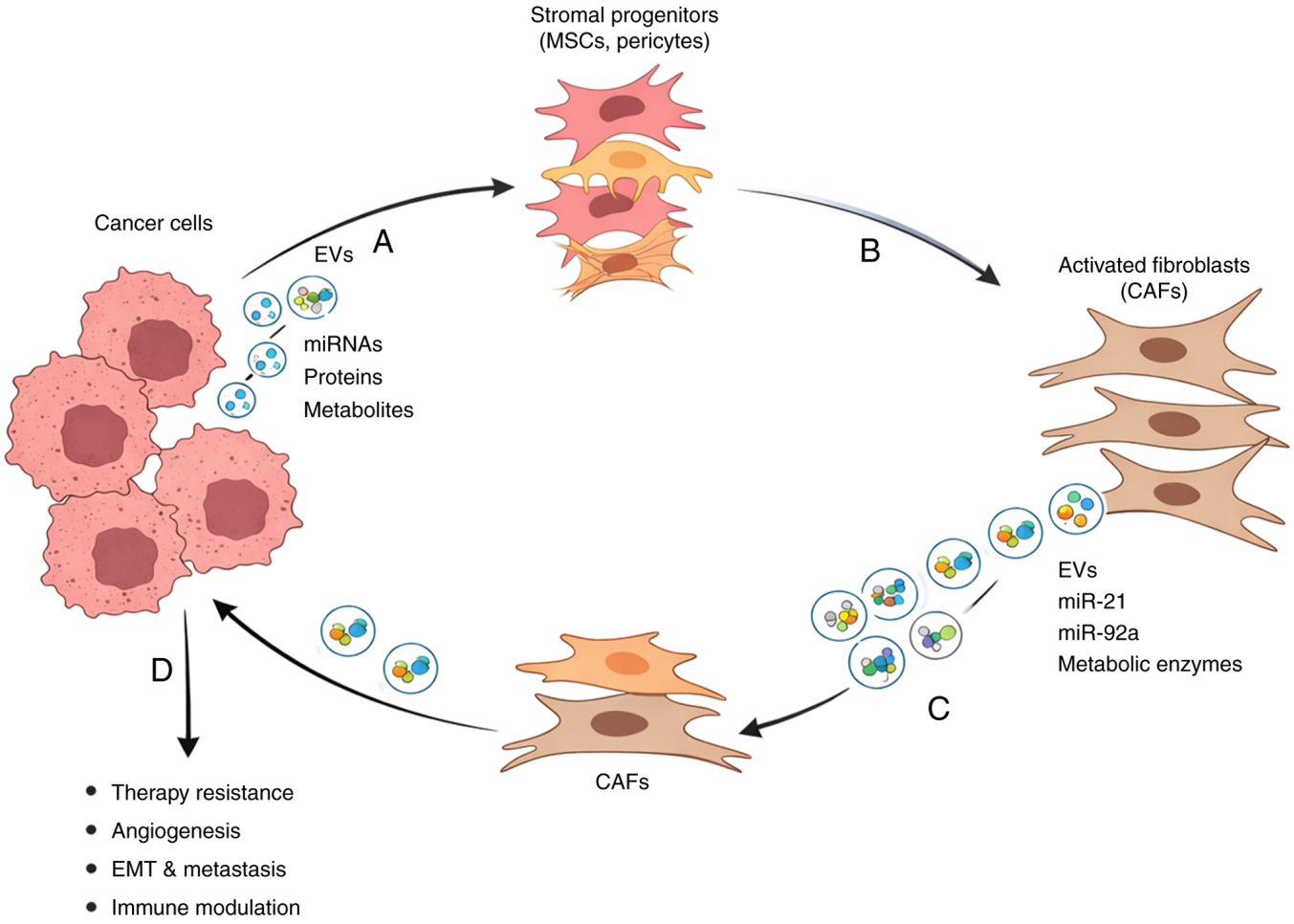

Figure 4. Role of EVs in tumor-stromal communication within the TME. (A) Cancer cells release EVs containing bioactive cargo such as miRNAs, proteins and metabolites into the TME. (B) These EVs are taken up by stromal progenitor cells, including MSCs and pericytes, leading to their activation and differentiation into CAFs. (C) Activated CAFs secrete their own EVs enriched with signaling molecules that are transferred back to cancer cells. (D) Uptake of CAF-derived EVs by cancer cells promotes tumor-supporting processes, including therapy resistance, angiogenesis, EMT, metastasis and immune modulation. CAF, cancer-associated fibroblast; EMT, epithelial-mesenchymal transition; EV, extracellular vesicle; miRNA/miR, microRNA; MSC, mesenchymal stromal cell; TME, tumor microenvironment.

by CAF-EVs promote resistance to fluoropyrimidine-based chemotherapy in colorectal cancer through Wnt/β-catenin activation and inhibition of apoptosis, whereas CAF-derived EVs enriched with miR-522 inhibit ferroptosis in gastric cancer cells, reducing chemotherapy sensitivity (114). There is also emerging evidence that CAF-derived EVs contribute to an immunosuppressive TME; EV cargo including immunomodulatory proteins and miRNAs is associated with reduced antitumor immune cell activity and remodeling of immune-relevant signaling, which may theoretically impact responses to immune checkpoint blockade therapies, although direct mechanistic evidence is still developing (115).

The clinical challenge of effectively translating stromal biology into cancer therapies is deeply rooted in the complex heterogeneity of CAF-derived EVs. This heterogeneity markedly constrains the development of targeted treatments and impacts patient outcomes. Evidence has indicated that CAF-derived EVs exhibit substantial cargo heterogeneity, reflecting the functional diversity of CAF subtypes (45). In addition to miRNAs and lncRNAs, CAF-derived EVs have been shown to carry distinct classes of non-coding RNAs, including circRNAs, which actively modulate tumor behavior (116). In a previous study, exosomes released from CAFs were reported to promote colorectal cancer progression through the transfer of circ_0067557, which upregulates Lin28A and Lin28B in recipient cancer cells, thereby enhancing malignant phenotypes (116). This example highlights a recurring mechanism whereby CAF-derived EVs frequently reprogram developmental pathways to fuel malignancy.

In addition to circRNAs, comprehensive analyses have revealed that EVs possess a complex and heterogeneous proteomic cargo, including signaling molecules, matrix-associated proteins and enzymes that mediate tumor-stroma interactions (117). This proteomic diversity facilitates multiple communication pathways within the TME. Furthermore, EV surface proteins such as integrins and tetraspanins (CD9, CD63, CD81) are essential for determining vesicle targeting, uptake and functional specificity in recipient cells, thereby enabling selective stromal-tumor communication (118,119). These proteins can be classified according to the specific hallmarks of cancer they support, which clarifies their functional hierarchy (120,121). For example, integrins are primarily involved in promoting invasion and metastasis by facilitating cell adhesion and migration. By contrast, tetraspanins such as

CD63 and CD81 contribute to immune evasion by modulating immune cell interactions and concealing tumor cells from immune detection (122,123).

A further dimension of complexity in CAF-derived EV signaling stems from the intrinsic heterogeneity of CAF populations. Advances in single-cell RNA sequencing and spatial transcriptomics are transforming the understanding of CAF diversity within tumors. Rather than constituting a single functional group, CAFs are now classified into distinct subtypes (iCAFs, myCAFs and ApCAFs), each characterized by unique transcriptional profiles and functional properties (37). This heterogeneity implies that CAF-derived EVs are not uniform but instead carry subtype-specific cargo that reflects their cellular origin. Recognizing these diverse effects is essential for interpreting the findings presented in the present review. Consequently, future research should focus on delineating the contributions of individual CAF subsets to EV-mediated signaling within the TME. Subtype-specific evidence is beginning to emerge; for example, exosomes from experimentally defined myCAFs have been shown to promote tumor cell stemness, migration and immune modulation through the transfer of specific lncRNAs such as PWAR6 (124). Nevertheless, direct comparative analyses of EVs from iCAFs, myCAFs or ApCAFs remain scarce (125). Most current studies continue to examine CAF-derived EVs as bulk populations without explicit subtype attribution, underscoring a notable gap in the field (125,126).

5. CAFs and their derived EVs as targets for cancer therapy

Early detection or diagnosis of cancer has been identified as one of the best ways to halt the spread of cancer and to ultimately treat patients (127,128). Biopsies are one of the foremost approaches used by cancer researchers in identifying the type and stage of cancer in individuals (129). Conventional biopsies, which involve the use of a sharp instrument or needle to collect a small portion of the tumor, are often invasive, painful and associated with a risk of infection (130). Liquid biopsies, which are non-invasive, can be performed as part of routine patient examinations, thereby increasing the likelihood that individuals with cancer will be diagnosed at earlier stages of the disease (130,131). Therefore, since EVs generated by cancer cells can be found in the circulation, it has been suggested that they can be isolated and analyzed as a form of liquid biopsy assay. For example, exosomes isolated from blood samples taken from patients with metastatic melanoma have been shown to be enriched in PD-L1, suggesting that the presence of PD-L1 in exosomes could potentially be used for diagnostic purposes (102). Distinct miRNAs expressed in exosomes have also been proposed as cancer biomarkers. Akers *et al* (132) demonstrated that miR-21 was highly expressed in exosomes from the cerebrospinal fluid of patients with glioblastoma, but was absent in exosomes from healthy individuals. These findings suggest that exosomal miRNA profiles could serve as reliable, non-invasive biomarkers for early cancer detection and classification. Furthermore, characterizing these EVs may inform personalized therapeutic strategies by identifying specific pathways for targeted anti-CAF interventions, thereby linking diagnostic insights with therapeutic applications.

Despite the promise of EVs as liquid biopsy biomarkers, a major technical challenge lies in distinguishing CAF-derived EVs from the abundant pool of circulating EVs originating from platelets, leukocytes and endothelial cells, which constitute the majority of EVs detected in blood (133,134). It is estimated that platelet-derived EVs account for 70-90% of circulating EVs, indicating the difficulty encountered when attempting to isolate the comparatively scarce CAF-derived EVs. Currently, to the best of our knowledge, no single surface marker uniquely identifies CAF-derived EVs in body fluids. Instead, emerging strategies rely on combinatorial marker profiling, integrating fibroblast-associated proteins, such as FAP, PDGFRβ, integrin α11 and caveolin-1, together with classical EV markers, including CD9, CD63 and CD81 (102,135). Advanced approaches combining immunoaffinity capture, high-resolution flow cytometry and single-vesicle analysis have shown promise in enriching stromal-derived EV subpopulations from plasma (136). These methodologies are still under optimization, however, they support the concept that CAF-derived EVs may serve as components of multi-analyte liquid biopsy platforms, rather than as standalone diagnostic biomarkers, highlighting the need for further standardization and clinical validation. Within this context, increasing attention is being directed toward CAF-derived EVs as complementary biomarkers, given their close involvement in tumor-stroma crosstalk and disease progression.

Efficient drug delivery has been shown to aid drug efficacy and specificity, and commonly used drug delivery systems include hydrogels, silica-based nanoparticles and synthetic liposomes. All of these have achieved success in drug delivery; however, they have notable limitations. For example, administration of nanoparticles and hydrogel-based therapeutics is frequently associated with adverse effects, including cytotoxicity and inflammatory responses (137). In addition, synthetic liposomes, while designed for drug encapsulation, often exhibit suboptimal cellular uptake, which diminishes treatment effectiveness (138). These challenges have necessitated the search for alternative drug delivery systems and led to the assessment of EVs as a delivery system, owing to the fact that they are produced by cells thus making them inherently biocompatible. Kamerkar *et al* (139) engineered exosomes derived from normal fibroblast-like mesenchymal cells to carry small interfering RNA or short hairpin RNA specific to oncogenic KrasG12D, a common mutation in pancreatic cancer. The results revealed that, compared with liposomes, the engineered exosomes (termed iExosomes) targeted oncogenic KRAS with an enhanced efficacy that was dependent on CD47-mediated interactions, which prevent macrophage clearance by providing a 'don't-eat-me' signal, thereby enabling immune evasion. Additionally, micropinocytosis enhanced the uptake of iExosomes by cancer cells, as this process is frequently exploited by cancer cells for nutrient acquisition (139). The results further showed that multiple mouse models of pancreatic cancer were suppressed by treatment with iExosomes, with overall survival ultimately improved (139). Although these engineered vesicles are not derived from CAFs, they establish proof-of-concept for the therapeutic application of fibroblast-origin EVs in tumor settings.

Chemotherapy, surgery and radiation therapy are the typical therapeutic modalities used to treat cancer depending

on the disease stage (140). However, a major challenge associated with chemotherapeutic strategies is the development of drug resistance, which frequently leads to tumor relapse and treatment failure. Xiao and Yu (14) posited that there is a notable therapeutic advantage in targeting the TME vs. directly targeting cancer cells, since cancer cells are prone to drug resistance due to their genomic instability, whereas non-tumor cells in the TME are genetically more stable and are more vulnerable. Notably, the past decade has seen an increasing appreciation of therapeutic approaches that re-engineer or reprogram the TME stroma into a quiescent state or even tumor-suppressive phenotype (141-143), which offers potential for translational impact in improving patient survival.

Immunotherapies, antiangiogenic medication, and treatments that target CAFs and the ECM are among the most common therapies directed at TME (15). Table II summarizes the major therapeutic strategies targeting CAFs and EV-mediated signaling within the TME, including their mechanisms of action, functional effects and current evidence levels. However, to ensure specificity and minimize off-target effects, it is crucial that these interventions focus on pathological phenotypic changes in TME-resident cells particularly CAFs and their EVs, rather than affecting similar cells in non-cancerous tissues. Consistent with this view, a recent systematic review (144) emphasized that although CAF-derived EVs, particularly exosomal-derived miRNAs, represent attractive therapeutic and biomarker candidates, their clinical translation is currently constrained by substantial biological and technical challenges. These include pronounced EV heterogeneity, overlap in vesicle composition across different stromal and tumor cell types, and the absence of definitive markers that allow unambiguous attribution of circulating EVs to CAF origin. Marker candidates such as CD63, CD81 and CD9 are being investigated as potential identifiers of CAF-derived exosomes, though their specificity to CAFs vs. other stromal cells is still under scrutiny. Consequently, it could be proposed that therapeutic strategies should prioritize modulation of CAF-derived exosomal signaling pathways rather than indiscriminate CAF depletion, thereby enabling selective interference with tumor-stroma communication while preserving the physiological functions of fibroblasts in normal tissues (144).

While there is an abundance of evidence on the tumor-promoting function of CAFs, including tumor growth, development and drug resistance via the secretion of various factors and EVs, emerging evidence has also suggested that CAFs can, in certain contexts, act to suppress tumor development and metastasis. Some subtypes of CAFs may facilitate the metastatic 'seed-and-soil' dynamics by either nurturing or restraining metastatic cells. This has led to the hypothesis that certain CAF populations may function as part of a host defense mechanism against neoplastic transformation (19,32,145). Studies focusing on mapping which CAF subtypes contribute to tumor progression vs. those that serve a protective role could deepen the argument for subtype-specific interventions. This necessitates further studies on CAFs as potential targets for cancer therapy, including direct targeting of CAFs, and indirect targeting through the various factors and EVs they secrete. Given the functional heterogeneity of CAFs, it is likely that a number of CAF- and EV-targeted therapeutic strategies preferentially affect specific CAF subpopulations rather than the entire CAF compartment (146,147). However, in numerous preclinical and clinical studies, the subtype origin of targeted CAFs or CAF-derived EVs is not explicitly defined, limiting precise attribution of therapeutic effects to iCAF or myCAF populations (148,149). A detailed comparison and characterization of these subtypes can reveal gaps that could be pivotal targets for future research.

From a therapeutic standpoint, disrupting the tumor exosome-fibroblast communication axis represents a potential strategy to prevent fibroblast reprogramming into tumor-promoting CAFs. Preclinical studies have explored multiple intervention points, including inhibition of EV biogenesis, which is the process of creating new vesicles, and release (150,151), blockade of vesicle uptake by recipient stromal cells (152), and interference with key surface molecules involved in EV internalization, affecting the entry of these vesicles into cells (153,154). Pharmacological inhibition of neutral sphingomyelinase, an enzyme that is involved in the breakdown of certain lipids, using agents such as GW4869 has been shown to markedly reduce exosome release from tumor cells and attenuate downstream stromal activation in experimental models (155,156). In addition, heparin and inhibitors of endocytic pathways, which are the routes by which cells internalize molecules and particles, have been reported to reduce EV uptake by fibroblasts and other stromal cells, thereby limiting exosome-mediated phenotypic reprogramming (157). However, despite these promising preclinical findings, no clinically approved therapies currently exist that specifically prevent tumor-derived exosome internalization by fibroblasts. This highlights both the therapeutic potential and the translational challenges associated with targeting EV-mediated signaling within the TME (122,158).

A major obstacle in cancer therapeutics is the effective translation of promising preclinical findings into successful clinical treatments. This challenge is underscored by the limited number of strategies that have advanced from preclinical studies to broad clinical application. In addition to EV-based approaches, several therapeutic strategies directly target CAF surface markers or signaling pathways. Among these, FAP has received considerable attention, as a serine protease that is highly expressed on activated CAFs in human tumors (159). Its enzymatic activity promotes tumor growth by degrading ECM components, thereby creating an environment favorable for cancer progression. Preclinical studies have indicated that immunotoxins targeting FAP can effectively eliminate FAP-positive CAFs *in vivo*, resulting in tumor suppression across multiple cancer models (160,161). Other therapeutic strategies targeting FAP include DNA vaccines (162) and chimeric antigen receptor-T-cell therapies (163). However, some studies have reported contradictory findings regarding FAP-targeted treatments. For example, FAP is also expressed by certain multipotent bone marrow stromal cells, which may be inadvertently targeted and eliminated by FAP-directed immunotoxins. This suggests that FAP-targeted drugs may have unintended effects on the bone marrow (164).

Table II. Therapeutic strategies targeting CAFs and EV-mediated signaling within the tumor microenvironment.

Therapeutic target/strategy	Targeted component	EV-related mechanism	Functional effect on tumor progression	Evidence level
GW4869	EV biogenesis	Inhibition of neutral sphingomyelinase; reduced exosome release	Attenuation of stromal activation	Preclinical
Heparin/endocytosis inhibitors	EV uptake	Blockade of vesicle internalization by stromal cells	Reduced CAF phenotypic reprogramming	Preclinical
iExosomes (engineered EVs)	KrasG12D (pancreatic cancer)	CD47-mediated delivery of siRNA/shRNA	Suppression of tumor growth; improved survival	Preclinical (proof-of-concept)
FAP-directed therapies (immunotoxins, CAR-T, vaccines)	Activated CAFs	Indirect suppression of CAF-derived EV signaling	Tumor suppression; limited benefit in phase II (colorectal cancer)	Preclinical; clinical (phase II)
GPR77 monoclonal antibodies	$CD10^{+}GPR77^{+}$ CAF subset	Suppression of CAF-mediated chemoresistance	Restored chemosensitivity (breast/lung cancer)	Preclinical
Vitamin D receptor (paricalcitol)	VDR on CAFs	Phenotypic reprogramming of CAFs	Increased chemo-efficacy; results currently inconclusive	Clinical (phase I/II)
PDGFR inhibition (imatinib)	CAF survival	Disruption of CAF-mediated support pathways	No significant clinical benefit observed in PDAC	Clinical (phase II)
CXCR4 antagonism (BL-8040 + pembrolizumab)	CAF-immune axis	Modulation of immunosuppressive environment	Improved chemotherapy outcomes in PDAC	Clinical (phase IIa)
Curcumin	CAF phenotype	Shift from pro- to antitumorigenic phenotype	Activation of immune cells; CAF reprogramming	Preclinical

CAF, cancer-associated fibroblast; CAR-T, chimeric antigen receptor T-cell; CXCR4, C-X-C chemokine receptor type 4; EV, extracellular vesicle; FAP, fibroblast activation protein; GPR77, G protein-coupled receptor 77; PDAC, pancreatic ductal adenocarcinoma; PDGFR, platelet-derived growth factor receptor; shRNA, short hairpin RNA; siRNA, small interfering RNA; VDR, vitamin D receptor.

Similar to FAP, targeting the GPR77, a C5a receptor on CAFs, using specific monoclonal antibodies has been shown to markedly enhance the response to chemotherapy; targeting the $CD10^{+}GPR77^{+}$ CAF subset with neutralizing antibodies has been shown to reduce CAF-mediated chemoresistance and restore chemosensitivity in preclinical breast and lung cancer models (31). Small molecules targeting receptors such as the vitamin D receptor on CAFs have been reported to boost the efficacy of chemotherapeutic agents (165,166), suggesting a moderate but consistent enhancement of treatment effects. Similarly, targeting the PDGFR has also been demonstrated to enhance chemotherapy impact, outlining its role in improving drug response. Natural compounds such as curcumin have been demonstrated to shift CAFs from a tumor-promoting phenotype to a more anti-tumorigenic state, while simultaneously activating peripheral blood mononuclear cells, although the precise quantitative effects require further study (167).

Grouping clinical studies based on their outcomes can provide valuable insights into their effectiveness. Firstly, among the negative outcomes, a FAP-targeting immunotoxin did not show sufficient therapeutic benefit in an early phase II clinical trial involving patients with advanced colorectal cancer (NCT02198274) (168). Similarly, imatinib, a PDGFR inhibitor, failed to demonstrate clinical benefit in patients with advanced pancreatic ductal adenocarcinoma (PDAC) in a multicenter phase II trial (NCT00161213) (169). Moving to inconclusive results, several phase I/II clinical trials have been conducted to investigate if paricalcitol, an analog of vitamin D2, will improve response to chemotherapies or immunotherapies in patients with PDAC, although a number of these trials are still awaiting conclusive results (155,166,170-172). Conversely, within the promising category, some combinations have shown more encouraging results. The phase IIa COMBAT clinical trial (NCT02826486) combining pembrolizumab, a programmed death 1 inhibitor, with BL-8040 (a CXCR4 antagonist) led to improved chemotherapy outcomes in patients with PDAC (173). While numerous CAF-related therapeutic targets have demonstrated potential in preclinical studies, only a few have successfully progressed into clinical trials. Babar *et al* (15) effectively summarized these trials, providing a comprehensive overview, including those on chemotherapeutic agents targeting CAFs and their EVs.

6. Conclusion

The use of EVs in cancer treatment holds promise, but it also presents several challenges that must be addressed. Several issues need further research and development to harness the full potential of EVs in cancer therapy. Current strategies targeting CAFs and CAF-derived EVs for tumor therapy have shown limited efficacy, which may be as a result of the fact that the origins of CAFs across cancer types remains unknown, as does the complete picture of subtypes and functional heterogeneity. Another challenge is minimizing unintended systemic and off-target effects associated with such targeted approaches.

Despite these limitations, EV-based strategies continue to offer opportunities for cancer treatment, particularly through the development of novel therapeutic platforms that combine conventional anticancer agents with approaches aimed at modulating CAF activity or CAF-derived EV signaling. Such combination strategies may enhance therapeutic efficacy while reducing resistance and tumor relapse. Consistent with this view, recent systematic evidence highlights that targeting CAF-derived exosomal communication, rather than CAF depletion alone, may represent a more feasible and biologically rational strategy for disrupting tumor-stroma crosstalk while preserving normal tissue homeostasis.

Finally, EV-based therapies have the potential to revolutionize cancer treatment and improve patient outcomes, particularly with respect to novel treatment strategies that combine existing anticancer agents and anti-CAF agents, which may be valuable and remain an area for cancer researchers to explore. Therefore, there is a need for further studies to improve the understanding of CAF biology, EV cargo heterogeneity and CAF subtype-specific EVs, with the aim of improving treatment outcomes through therapies targeting CAF-derived EV.

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Authors' contributions

USN and CAGR conceived and designed the study. USN and JEO developed the figures and visual content. The initial draft of the manuscript was written by USN, JEO and BRRC. BRRC and CAGR critically reviewed and revised the manuscript for intellectual content. MAA and IS conducted the final review and approved the manuscript for submission. All authors were involved in the design, review and approval of the final version of the manuscript, and agree to be accountable for all aspects of the work. Data authentication is not applicable. All authors read and approved the final manuscript.

Ethics approval and consent to participate

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Competing interests

The authors declare that they have no competing interests.

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