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REVIEW

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Cancer associated fibroblasts in cancer development and therapy

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Abstract

Cancer-associated fibroblasts (CAFs) are key players in cancer development and therapy, and they exhibit multifaceted roles in the tumor microenvironment (TME). From their diverse cellular origins, CAFs undergo phenotypic and functional transformation upon interacting with tumor cells and their presence can adversely influence treatment outcomes and the severity of the cancer. Emerging evidence from single-cell RNA sequencing (scRNA-seq) studies have highlighted the heterogeneity and plasticity of CAFs, with subtypes identifiable through distinct gene expression profiles and functional properties. CAFs influence cancer development through multiple mechanisms, including regulation of extracellular matrix (ECM) remodeling, direct promotion of tumor growth through provision of metabolic support, promoting epithelial-mesenchymal transition (EMT) to enhance cancer invasiveness and growth, as well as stimulating cancer stem cell properties within the tumor. Moreover, CAFs can induce an immunosuppressive TME and contribute to therapeutic resistance. In this review, we summarize the fundamental knowledge and recent advances regarding CAFs, focusing on their sophisticated roles in cancer development and potential as therapeutic targets. We discuss various strategies to target CAFs, including ECM modulation, direct elimination, interruption of CAF-TME crosstalk, and CAF normalization, as approaches to developing more effective treatments. An improved understanding of the complex interplay between CAFs and TME is crucial for developing new and effective targeted therapies for cancer.

Keywords Cancer associated fibroblasts (CAFs), Extracellular matrix (ECM), Tumor microenvironment (TME), Cancer development, Cancer therapy, Heterogeneity

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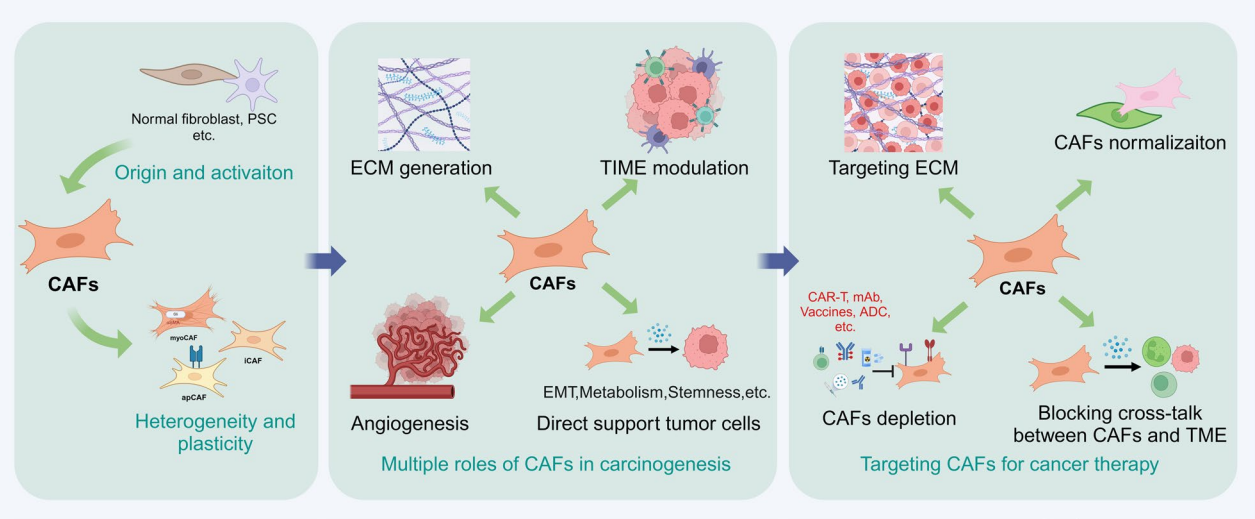
Graphical abstract



Introduction

During the development of the mammalian embryo, normal fibroblasts (NFs) that are important for forming connective tissues of the body can originate from the primitive mesenchyme and share a common embryonic lineage with other mesenchymal cell types, such as adipocytes, chondrocytes, and osteoblasts [1]. In normal physiological conditions, fibroblasts serve as primary contributors to the extracellular matrix (ECM) of connective tissues and are central to the process of tissue repair during stress and in injury states where, in such situations, these cells are activated in response to signals and tissue damage [2–4]. Beyond their reparative roles, fibroblasts also facilitate angiogenesis by secreting vascular endothelial growth factor A (VEGFA) [5–7], as well as orchestrate immune system functions through the release of chemokines and cytokines [7–11].

In cancer states, fibroblasts are known to constitute a significant component of the tumor stroma. Moreover, fibroblasts within tumors have been found to undergo phenotypic as well as functional transformation, typically observed as a result of interactions with resident tumor

Table 1 Frequently used makers for identifying CAFs

Marker	Biological function	Functions of CAFs	Specificity	Refs
PDPN	Transmembrane glycoprotein involved in cellular adhesion and signaling	Promotes resistance to EGFR-TKIs; initiates tertiary lymphoid structure (TLS) formation	Expressed in epithelial tumor cells, inflammatory macrophages, and CAFs	[19, 91,92,138, 204]
FSP1/S100A4	Calcium-binding protein that regulates cell motility and metastasis	Modulates malignant cell metabolism via FAK-mediated pathways; expression correlates with poor prognosis	Highly expressed in prostate cancer and breast cancer (BC)	[15, 21, 22, 32, 129]
PDGFRα/β	Tyrosine kinase receptors that mediate growth factor signaling	Drives immune suppression, angiogenesis, and hormone therapy resistance	Expressed on fibroblasts, neural progenitors, pericytes, and astrocytes	[16, 115, 122, 163, 252]
αSMA	Highly conserved protein essential for cytoskeletal integrity and contractility	Defines myofibroblast contractility; regulates ECM remodeling	Expressed in smooth muscle cells, pericytes, and activated CAFs	[4, 17, 18, 42]
FAPα	Type II transmembrane serine protease whose expression is linked to tissue repair and fibrosis	Remodels ECM; suppresses immunity; expression is associated with poor prognosis	Expressed during wound healing, in fetal placenta, and CAFs	[77, 87, 100, 160–162, 173, 176]

cells and, as such, these "cancer-associated fibroblasts (CAFs)" have been found to influence the tumor microenvironment (TME) [13, 14]. Despite our current understanding of CAFs, their precis identification continues to pose a challenge, owing to a lack of definitive molecular markers that distinguish them from other cells, as well as from embryonic mesenchyme [15–18]. Indeed, molecular markers such as α-SMA, fibroblast activation protein (FAP), platelet-derived growth factor receptor (PDGFR) and podoplanin (PDPN), have all been employed to facilitate the identification of CAFs [19–22]. Typically, these markers are combined with lineage markers to enable negative selection, through the exclusion of epithelial cells, tumor cells, myeloid-derived cells, endothelial cells [23, 24]. A list of typical molecular markers for CAFs is provided in Table 1.

The importance of CAFs in cancer development is underscored by their roles in multiple hallmarks of cancer, including ECM formation, tumor cell proliferation, invasion, metastasis, angiogenesis, and immune suppression [13]. Moreover, the heterogeneity of CAFs within the TME adds a further dimension of complexity to their functions [25]. Studies using single-cell RNA sequencing (scRNA-seq) have identified distinct subsets of CAFs that feature unique gene expression profiles and functional properties. These subsets, such as myofibroblastic CAFs (myoCAFs), inflammatory CAFs (iCAFs), and antigen-presenting CAFs (apCAFs), have been found to influence tumor progression and immune responses in different ways, through a variety of mechanisms including the secretion of specific cytokines, chemokines, and ECM components [26–30].

In this review, we comprehensively describe the multifaceted roles of CAFs in cancer development. Moreover, we focus on the latest findings on the complex heterogeneity of CAFs and plasticity within the TME. Also, we review the potential for CAFs as therapeutic targets, discuss the emerging strategies to target CAFs in cancer treatment. Taken togther, through our exploration of the complex interplay between CAFs and the TME, we bring attention to current efforts that could lead to the development of more effective and targeted therapies for cancer.

Origins of CAFs and their activation

CAFs are known to derive from resident fibroblasts within normal tissues, however they have also been described to arise from the cellular transformation of adipocytes, pericytes, stellate cells, pericryptal cells, mesothelial cells, mesenchymal stem cells (MSCs) [31–34]. Continuous observations of the transformation process, from normal epithelia to atypical hyperplasia to invasive carcinoma, have revealed a concomitant proliferation and dysfunction of fibroblasts. Notably, cultured NFs have been found to be transformed into CAFs under certain conditions, such as when exposed to conditioned media (CM) derived from tumor cells, or under hypoxia conditions, or upon exposure to TGFβ, or through the addition of cancer-derived exosome preprations [35–38]. For example, in breast cancer (BC), resident human mammary fibroblasts can transform into myoCAFs via autocrine TGF-β which binds to TGF-β I/II receptor and activates TGFβ/Smad signaling pathway. Moreover, such signalling in these cells also promotes CXCL12 secretion, which additionally forms a positive feedback loop through CXCR4 stimulation. Thus, TGF-β and CXCL12 concurrently induce myoCAFs through an autostimulatory mechanism as well as through their signalling cross-communication [39].

In addition to myoCAFs, studies have shed light on the origins of other CAFs subtypes. For example, in mouse models of colitis-associated colorectal cancer (CRC), it has been reported that cells expressing the pericryptal leptin receptor (Lepr) proliferate and transform to CAFs that express the melanoma cell adhesion molecule (MCAM), and such CAFs promote an immune suppressive TME [40, 41]. In separate scenario, pancreatic stellate cells (PSCs), when activated, transform into αSMA-expressing CAFs that secrete factors that promote tumor growth, cell survival, and metastasis [42]. Moreover, in pancreatic ductal carcinoma (PDAC), mesothelial cells have been found to transform into apCAFs under the regulation of IL-1 and TGFβ, and this was associated with downregulation of mesothelial features and upregulation of fibroblastic features [43]. Also, in prostate cancer, TGF-β1 secreted by tumor cells and tumor stroma recruits MSCs to the tumor tissue site and induce their differentiation into CAFs [44]. Furthermore, in breast cancer, Wnt3a derived from tumor cells induces adipocytes to transform into adipocyte-derived fibroblasts (ADFs) [32]. In ovarian cancer, Eckert et al. discovered through a proteomic analysis study that Nicotinamide N-methyltransferase (NNMT) expression is essential for the functional aspects of cancer-associated fibroblasts (CAFs), including their expression of CAF markers, cytokine secretion characteristics, and their production of carcinogenic extracellular matrix molecules. Mechanistically, the expression of NNMT in CAFs leads to S-adenosylmethionine (SAM) depletion, reduced histone methylation, and widespread gene expression changes in cells of the tumor stroma. Accordingly, knockdown of NNMT in CAFs resulted in morphological changes such that they more closely resembled normal stromal fibroblasts, and this visual feature was

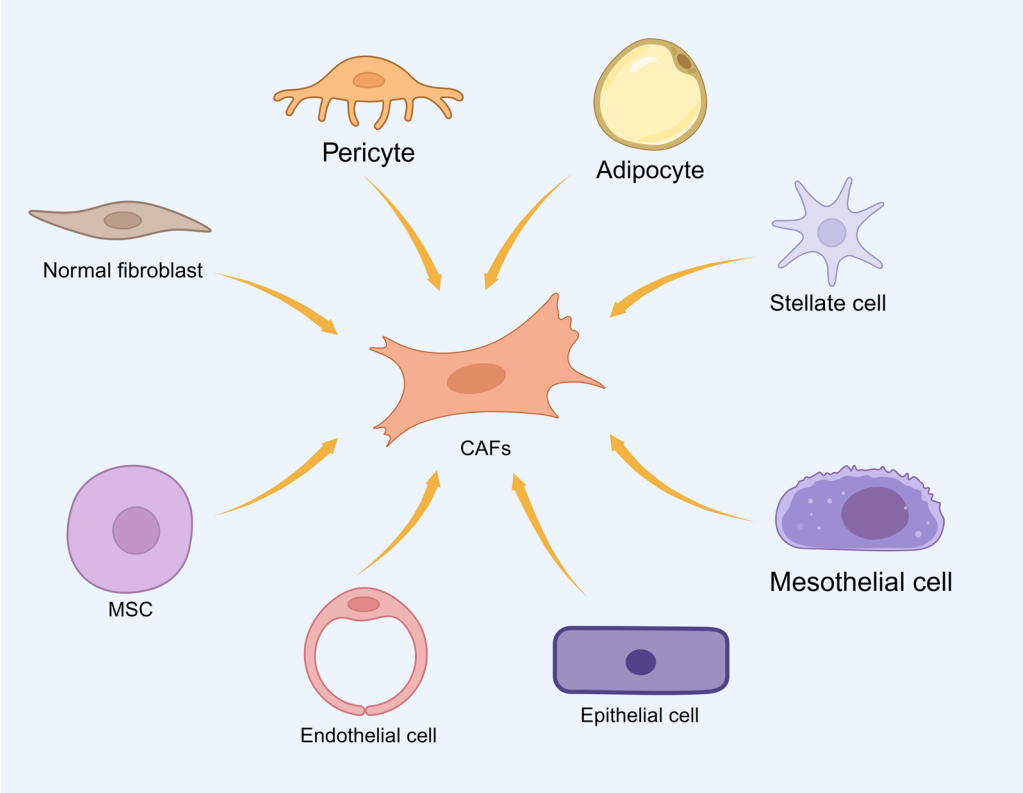


Fig. 1 Origins of CAFs. CAFs may originate from various cell types including pericytes, adipocytes, stellate cells, mesothelial cells, epithelial cells, endothelial cells, mesenchymal Stem Cells (MSCs) and normal fibroblast. This figure was created with BioRender.com

concomitant with a reduction in the expression of CAF markers [45]. Taken together, these examples showcase the diverse cellular origins for CAFs and how each distinct CAF subtype shapes their functional specialization within the TME (Fig. 1). This topic is further explored below.

Approaches to studying CAFs

The approaches to studying CAFs can be considered to comprise four interconnected strategies, namely: (1) isolation via primary culture or cytokine-induced differentiation [42, 46, 47] (Fig. 2A); (2) animal models such as genetically engineered mouse models (GEMMs) (e.g., KPC model for PDAC) that model spontaneous carcinogenesis and enable conditional CAFs depletion as well as xenograft transplantation [48–53] (Fig. 2B); (3) in vitro systems (2D/3D co-culture, CM analysis, organoids) or in vivo co-implantation to dissect tumor-CAF interactions at the cellular and molecular levels [54–61] (Fig. 2C); (4) combinations of classical techniques (such as immunohistochemistry, flow cytometry) with emerging tools (such as scRNA-seq and spatial transcriptomics (ST)) to reveal complex molecular functions of CAFs within the tumor microenvironment [62] (Fig. 2D).

Multifaceted roles of CAFs in cancer development

Modulation of the ECM

CAFs are the primary contributors to ECM formation through synthesis and deposition of collagen fibers [32]. A study analyzing collagen expression across distinct CAFs subtypes has elucidated that CAF subtypes possess unique collagen expression profiles. For example, myoCAFs are characterized by the expression of collagens such as COL10A1 and COL11A1, while iCAFs predominantly express COL14A1 [26]. In another example, Lambrechts et al. performed a scRNA-seq to define five CAFs clusters in non-small cell lung cancers (NSCLCs). Cluster 1 expressed COL10A1 and shows high expression of ECM proteins and TGF-β-related genes, while Cluster 2 was found to express COL4A1, along with high levels of ACTA2, MEF2C, MYH11 expression [62]. Through their role in ECM deposition, CAFs can create a physical barrier that hinders the entry of immune cells as well as therapeutic agents into the tumor tissue and, as such, protect tumor cells from immune system attacks and anti-tumor treatment [47] (Fig. 3A).

The ECM remodeling mediated by CAFs is also known to influence tumor invasion. CAFs can secrete matrix metalloproteinases (MMPs), which are zinc-dependent

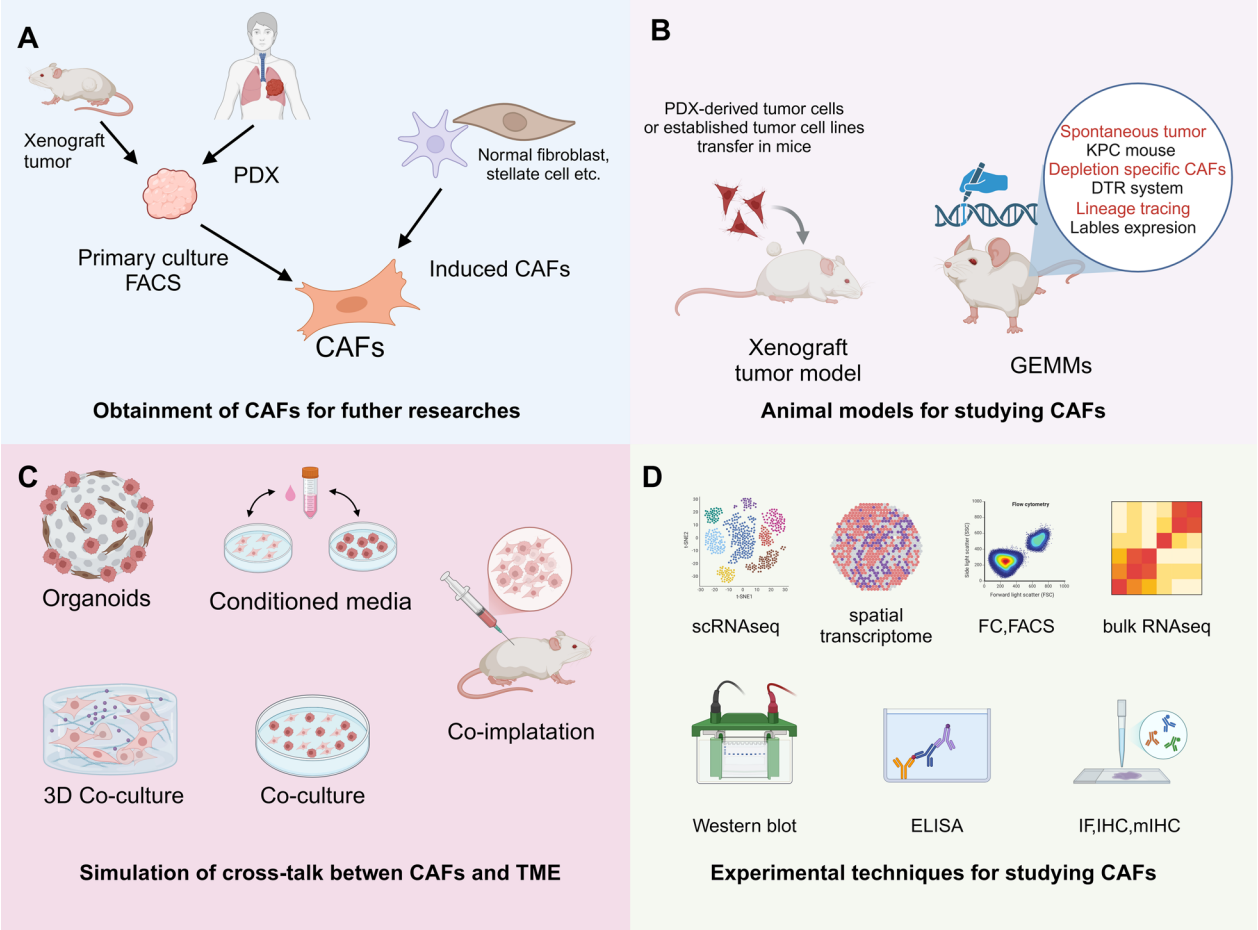


Fig. 2 Methodology for studying CAFs. (**A**) CAFs may be obtained through primary culture, or transformation from other cells, such as normal fibroblasts or pancreatic stellate cells (PSCs), for further researches. (**B**) Animal models of CAFs include patient-derived xenografts (PDX) and transplanted tumor models established from cell lines. Genetically engineered mouse models (GEMMs) can spontaneously develop tumors, better simulating the interaction between CAFs and TME. These genetically engineered mice also allow for the specific elimination of CAF subsets using drugs such as diphtheria toxin, as well as lineage tracing of CAF subsets through the expression of specific markers. (**C**) In vitro approaches to study CAF-TME interactions include 2D/3D co-culture, conditioned media transfer, and tumor organoid models. In vivo methods involve co-inoculation of CAFs and tumor cells. (**D**) CAF research integrates techniques such as western blotting (WB), flow cytometry, and immunofluorescence. Advanced tools like single-cell RNA sequencing (scRNA-seq) and spatial transcriptomics provide deeper functional insights. This figure was created with BioRender.com

endopeptidases that degrade ECM components such as collagens, fibronectin, elastin and laminin, so as to facilitate stromal degradation and tumor cell invasion [63, 64]. Studies of cocultures of carcinoma cells and stromal fibroblasts have revealed that fibroblasts predominantly serve as lead cells during invasion, while carcinoma cells trail behind, navigating along pathways in ECM generated by the lead fibroblasts. As such, fibroblasts are shown as pivotal for facilitating cancer cell invasion through a mechanims that involves protease-driven and force-mediated reorganization of the ECM [65]. Of the molecular players involved, caveolin-1 (Cav1) is a membrane-associated protein that plays a crucial role cell signaling in the process, as well as in ECM reconstruction, and tumor progression [66]. Indeed, expression of Cav1 in CAFs enhances cell elongation in 3D cultures via p190RhoGAP, promoting force-dependent contraction, matrix alignment. Cav1-deficient mice exhibit stromal disorganization, while Cav1-rich stroma in human carcinomas and melanoma metastases promotes tumor aggressiveness [60]. Moreover, GP130-IL6ST and JAK1 stimulate RhoA-dependent actomyosin contractility in both tumor cells and CAFs, leading to matrix reconstruction and enhanced tumor cell migration. Notably, inhibition of the signaling axis that comprises these key factors

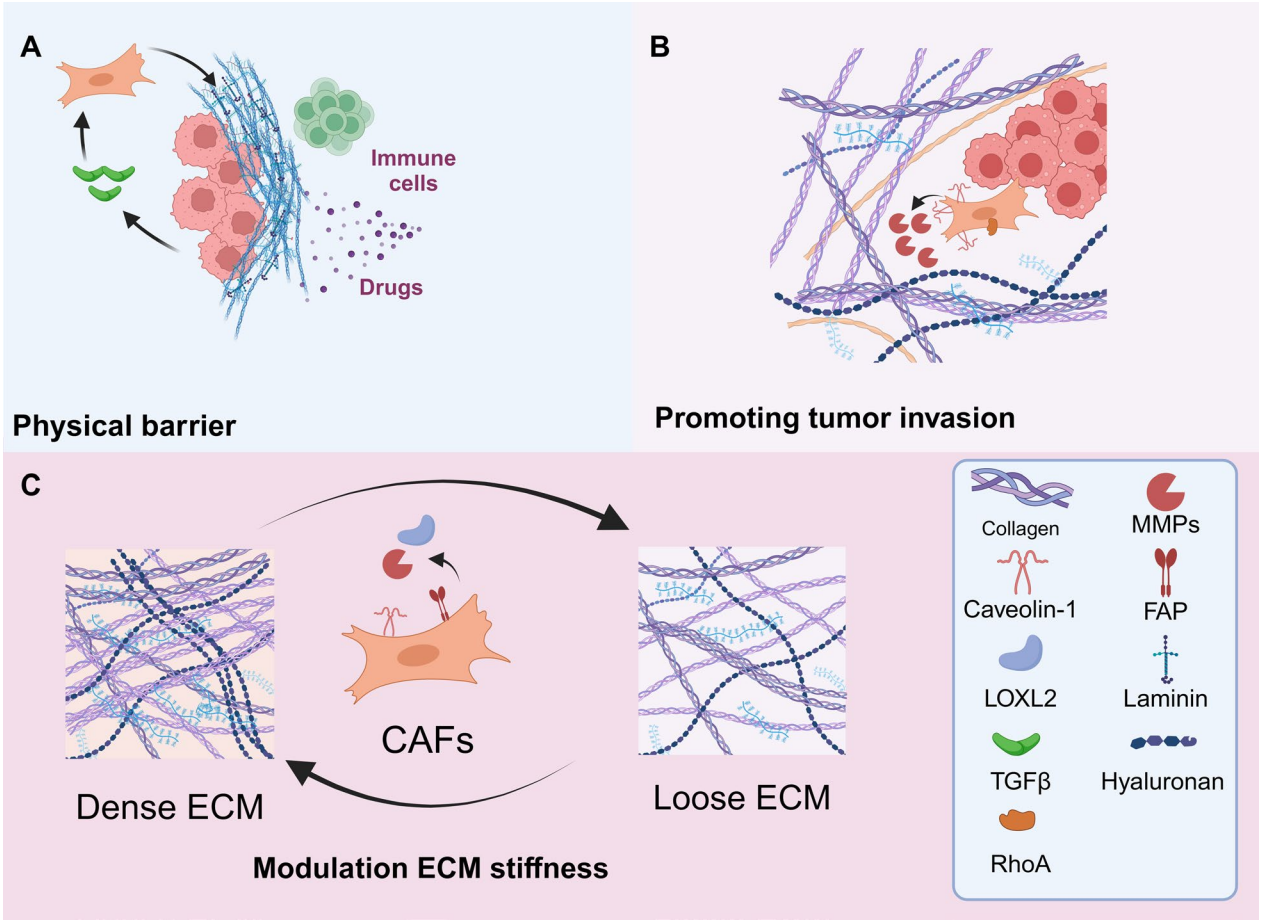


Fig. 3 CAFs modulate ECM to promote tumor growth. (**A**) CAFs promote the deposition of extracellular matrix, forming a physical barrier that hinders immune cell infiltration and drug penetration, thereby creating obstacles for anti-tumor treatment. (**B**) CAFs remodel ECM, facilitating tumor cell invasion and metastasis. (**C**) CAFs regulate the balance between dense ECM and loose ECM, thus promoting cancer progression. This figure was created with BioRender.com

may be crucial for developing interventions that effectively block tumor cell invasion [67] (Fig. 3B).

The balance between ECM deposition and degradation is crucial for maintaining ECM homeostasis, but this balance can be dysregulated in tumor microenvironments [68] (Fig. 3C). Moreover, CAFs secrete enzymes that facilitate collagen cross-linking which, in turn, further enhances the rigidity of the ECM. The stiffness of tumor tissues is generally significantly higher than that of normal tissues [69], and this stiffness of the ECM has been shown to promote tumor progression by restricting drug penetration, limiting the infiltration of immune cells, and activating signaling pathways such as integrin-mediated focal adhesion kinase (FAK/SRC) signaling as well as mechanotransduction pathways (e.g. Rho-GTPase, ERK, YAP/TAZ) [70–72]. For instance, studies of the impact of stiffness on cultured intrahepatic cholangiocarcinoma (ICC) and hepatocellular carcinoma (HCC) cells showed that numbers were higher at 16 kPa stiffness rather than at 2 kPa, and that such cells appearred more robust and appeared to be accompanied by features such as a more regular actin arrangement and higher YAP1 content [69]. In a cohort of 107 colorectal cancer patients, the median overall survival (OS) of the low-stiffness group was significantly longer than in the high-stiffness group (54.38 ± 2.64 months vs 64.05 ± 1.00 months, $P = 0.007$) [73]. Recently, Zheng et al. revealed that in PDAC, matrix stiffness could drive tumor proliferation through glycolytic metabolism via upregulated CLIC1 expression mediated by the Wnt/β-catenin/TCF4 signaling pathway [74]. Through digital pathology analysis, Maiques et al. found that the morphology of extracellular matrix fibers increased from the tumor core to the invasive front, and that fibres appeared longer and denser. The changes in fibers at the invasive front induced tumor cell cytoskeletal reconfiguration through the Rho-ROCK-MLC2 pathway, and promoted cell contraction, reduced adhesion, and induced pseudopod-like behaviors. In

another example, it was reported that a "mechanical-inflammation signature" (MIS) gene set was upregulated at the invasive front and associated with poor patient prognosis [75]. Zheng et al. found through scRNA-seq that PDGFRα + ITGA11 + CAFs are associated with vascular invasion and lymph node metastasis in early-stage bladder cancer by promoting collagen deposition as well as enhancing the migratory ability of tumor cell spheroids via the glycoprotein CHI3L1. Notably, treatment that combined CHI3L1-neutralizing antibodies and ITGA11-neutralizing antibodies could inhibit vascular invasion in early BC [76]. While the current evidence largely supports the notion that ECM stiffness exerts a tumor-promoting effect, a few studies have conversely found that a reduction in ECM components could facilitate tumor progression [77–79]. For example, in PDAC models, an anti–lysyl oxidase like-2 (anti-LOXL2) antibody decreased matrix content and this was associated with accelerated tumor growth and lower tissue stiffness [78]. One possible explanation is that ECM remodeling involves intricate signaling networks, such that a reduction in ECM stiffness caused by specific factors might paradoxically trigger compensatory pro-tumorigenic signaling pathways. For example, Hedgehog signaling blockage reduces the stroma in PDAC, but accelerates tumor progression through increased blood vessel formation [80]. Further research is needed to further clarify these issues.

Components of the ECM, such as CTGF and integrins, play complex roles in signal transduction. For example, blocking CTGF signaling can enhance the efficacy of chemotherapy without altering the effective concentration of gemcitabine, through an effect that is accompanied by a reduction in the expression of X-linked inhibitor of apoptosis protein (XIAP) [81]. Remarkably, a recent study shows that in PDAC organoids, hyaluronic acid (HA) interacts with the CD44 receptor which, in turn, promotes the expression of drug efflux transporters, leading to chemotherapy resistance. Moreover, this resistance can be reversed by transferring the organoids from high-stiffness to low-stiffness matrices, and such findings offer a novel strategy for improving chemotherapy resistance by targeting the ECM [82].

CAFs interact with multiple immune cell types within the TIME (Tumor immune microenvironment)

CAFs have been found to have interactions with multiple immune cell types in the TIME, including effector T cells, regulatory T cells (Tregs), tumor associated macrophages (TAMs), tumor associated neutrophils (TANs), and myeloid derived suppresor cells (MDSCs) [83, 84], as explained further below.

Effector T cells and Tregs

CAFs can inhibit the functions of effector T cells through the production of immunosuppressive factors such as IL-6, CXCL9, CXCL12 and TGFβ, and by direct cell–cell interaction through PD-1/PD-L1 receptor signaling [36, 85, 86] (Fig. 4A). In PDAC that arises in the KPC mouse model, CXCL12 secreted by FAPα + CAFs is the primary cause of immunosuppression, where CD8 + T cells do not respond to anti-CTLA-4 and anti-PD-L1 therapies [87]. In studies of human esophageal carcinoma, the numbers of CAFs are negatively associated with the presence of CD8 + tumor infiltreated lymphcytes (TILs). Co-implantation of CT26 cells and CAFs have been shown to result in accelerated tumor growth, accompanied with decreased CD8 + T cells and increased FoxP3 + TILs [88]. Recently, a study that utilised ST and scRNA-seq by Song et al. revealed that CAFs suppress the infiltration and function of effector T cells by expressing CXCL12 and PD-L1, a mechanism maintained via autocrine IGF2. This finding is consistent with clinical studies that show that high expression of IGF2 is associated with suboptimal outcomes of anti-PD-1 therapy. Indeed, targeting the IGF2/IGF1R signaling pathway with the inhibitor linsitinib can significantly enhance the efficacy of immune checkpoint inhibitors (ICIs) [89].

Although the immunosuppressive roles of CAFs are well appreciated, some studies also suggest certain subgroups of CAFs may even play an immune promotive role. In PDAC, depletion of αSMA + myofibroblasts led to invasive, undifferentiated tumors with increased CD4 + Foxp3 + Tregs, suggesting their role in promoting anti-tumor immunity [90]. A subgroup of PDPN + CAFs were reported to be able to induce the initiation and expansion of tertiary lymphoid structures (TLSs) that could enhance the efficiency of immune surveillance and locally potentiate immune responses against tumor antigens. Notably, these TLSs were found to often correlate with increased numbers of mature dendritic cells and robust T-cell infiltration [91, 92]. Through scRNA-seq and ST analysis of HCC samples, it was found that tumors from patients with a good response to immunotherapy exhibited more infiltration of CCL19 + fibroblasts and plasma cells. This co-localization was associated with T-cell infiltration and the formation of TLSs. In contrast, in immune-exclusion samples, DKK1 + tumor cells accumulated at the tumor boundary, inhibiting the infiltration of CCL19 + fibroblasts and plasma cells into the tumor area [93]. Thus, the interactions between CAFs and effector T cells and Tregs remain to be better understood.

Tumor-associated macrophages (TAMs)

CAFs can recruit and induce monocyte differentiation into M2-like TAMs through cytokines such as CXCL12,

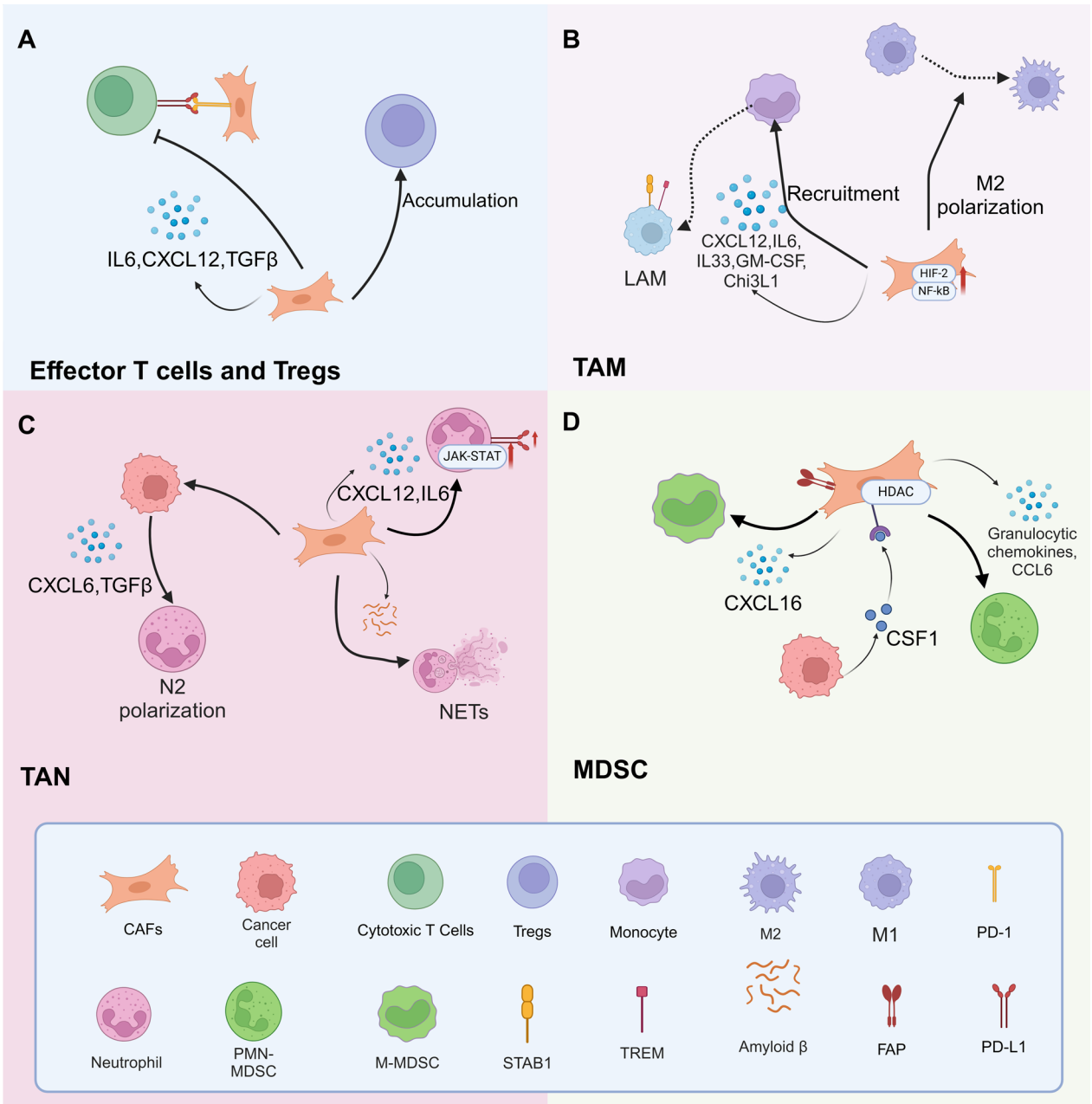


Fig. 4 CAFs modulate the tumor immune microenvironment (TIME). (**A**) CAFs inhibit the function of effector T cells by secreting IL-6, CXCL12, TGF-β, and by expressing PD-L1; they also recruit regulatory T cells (Tregs). (**B**) CAFs recruit macrophages through cytokines such as IL-6, CXCL12, and IL-33, and promote M2 polarization and inducing immunosuppresive subses like lipid-associated macrophages (LAMs). (**C**) CAFs promote N2 polarization of TANs, upregulate PD-L1, and stimulate neutrophil extracellular trap (NET) formation. (**D**) CAFs enhance infiltration of monocytic (M-MDSCs) and polymorphonuclear myeloid-derived suppressor cells (PMN-MDSCs) via tumor-derived CSF-1. This figure was created with BioRender.com

CCL5, IL-6, IL-33, GM-CSF and glycoprotein Chitinase-3-like-1 (Chi3L1) [41, 94–99] (Fig. 4B). Besides, CAFs increase macrophage adhesion through interactions between the class A scavenger receptor (SR-A/CD204) and cleaved type I collagen, which is selectively cleaved by FAP expressed on CAFs [100]. Furthermore, in triple negative BC (TNBC), CAFs recruit and reprogram blood monocytes into an immune suppressive lipid associated macrophage (LAM) subset via the CXCL12–CXCR4 axis, which is marked by STAB1 as well as high TREM2

expression. This LAM subset has been reported to be expanded in patients refractory to immune checkpoint blockade (ICB). In preclinical models, genetic depletion of these LAMs leads to TNBC tumor growth suppression [101].

HIF2 expression in CAFs is known to induce the immunosuppressive environment of PDAC. Studies using scRNA-seq have showed that recruitment of MDSC in CAF-HIF2 knockout tumors was inhibited in this context. Accordingly, the proportion of M2-polarized TAMs were decreased in CAF-HIF2 knockout tumors [52]. In HCC, POSTN + CAFs attract and induce macrophages to SPP1 + TAM via the IL-6/STAT3 signaling pathway, which in turn hinders the effective infiltration of T-cells and diminishes the efficacy of immunotherapy. Patients with increased expression of both POSTN + CAFs and SPP1 + macrophages showed poorer therapeutic outcomes in an immunotherapy cohort [102]. Similarly, in the case of gastric cancer (GC), it has been shown that thrombospondin 2 (THBS2)-expressing matrix CAFs (mCAFs) promote the recruitment of peritoneum-specific macrophages, which then differentiate into SPP1 + TAMs through the C3-C3AR1 axis which, in turn, disrupts this signaling axis and enhances the efficacy of ICIs [103].

The interplay between CAFs and TAMs is reciprocal, such that TAMs also affect the functions of CAFs. In PDAC, IL-33-stimulated macrophages secret CXCL3, which induce the transition of myoCAFs and upregulates α-SMA expression thorugh activation of the CXCL3–CXCR2 signaling pathway [104]. M2 polarization of TAMs increases their capability to modulate the EMT in CAFs, resulting in their enhanced reactivity [105].

Tumor-associated neutrophils (TANs)

In HCC, CAFs secrete CXCL12, which recruits neutrophils and also upregulates their PD-L1 expression via a IL6-JAK-STAT3 signaling pathway. These activated PD-L1 + neutrophils exert a tumor-promoting effect by suppressing T-cell immunity [106]. Similar findings were reported in GC, in that myeloid stem cells differentiate into CAFs upon stimulation from neutrophils. The former reciprocally activate neutrophils through IL-6–STAT3–ERK1/2 signaling cascade [31]. Moreover, CAFs produced cardiotrophin-like cytokine factor 1 (CLCF1), which stimulated the secretion of CXCL6 and TGF-β from tumor cells. These secreted factors subsequently facilitated TAN infiltration and N2 polarization through a paracrine mechanism [107].

In addition to secretion of CXCL12, CAFs are known to secrete amyloid β to stimulate the formation of neutrophil extracellular traps (NETs) by a reactive oxygen species (ROS)-mediated pathway, which facilitates tumor progression [108]. Also, pancreatic cancer cells can trigger the formation of NETs, which subsequently induce hepatic stellate cells into CAFs. In liver metastasis mouse models, DNase I, an inhibitor of NETs, effectively suppressed the occurrence of liver metastasis in vivo (Fig. 4C) [109].

Myeloid-derived suppressor cells (MDSCs)

In liver cancer, CCL2 secreted by FAP + CAFs could promote tumor growth by enhancing the recruitment of MDSCs via a STAT3 signaling pathway, which is abolished in Ccr2-deficient mice or by exposure to the CCR2 inhibitor, sc-202525 [46, 110]. By secreting CXCL16, CAFs attract monocytes that then differentiate into monocytic MDSCs, activating the tumor stroma and exacerbating TNBC aggressiveness [111]. The expression of granulocytic chemokines in CAFs is downregulated by HDAC2, induced by tumor cell derived CSF1. This downregulation restricts the migration of polymorphonuclear myeloid-derived suppressor cells (PMN-MDSCs) towards tumors. Interventions with CSF1R inhibitors disrupt this crosstalk, leading to a marked enhancement in the recruitment of PMN-MDSCs to tumor sites which, in turn, contributes to immunosuppression [112–114] (Fig. 4C).

Angiogenesis

CAFs are capable of secreting a variety of angiogenic regulators such as VEGFA, platelet-derived growth factor-C (PDGF-C), fibroblast growth factor 2 (FGF2), CXCL12, and WNT2 [115–120]. A study by Orimo et al. found that CAFs co-planted with human BC MCF-7 cells resulted in significantly increased tumor vascular density. Further analysis revealed that CAFs could recruit endothelial progenitor cells (EPCs), a bone-marrow derived stem cell population, into the tumor by releasing CXCL12 which, in turn, resulted in an increase in the number of EPCs within the tumor. Experiments using in vivo approaches have found that, this process of EPC recruitment into tumors could be inhibited by neutralizing antibodies against CXCL12, thereby inhibiting tumor growth [121]. In a separate study utilising a CRC xenograft mouse model, overexpression of WNT2 resulted in increased tumor vessel density and tumor volume. Mass spectrometry and cytokine array analyses collectively revealed that WNT2 overexpression resulted in upregulation of the expression proteins associated with pro-angiogenic functions, including extracellular matrix molecules, ANG-2, IL-6, G-CSF, and placental growth factor (PGF) [120]. A cohort study of 535 prostate cancer

patients who underwent surgery showed that PDGFRβ is expressed in the stromal tissues of prostate cancers, and that high expression was associated with poor prognosis [122]. Moreover, in a cervical cancer model, PDGF expressed by cancer cells activate PDGFR on CAFs, and this promoted their release of FGF which, in turn, enhanced angiogenesis. Studies have shown that inhibition of PDGFR signaling with a small molecular inhibitor Imatinib could be effective to suppress the growth of invasive carcinomas [115, 123, 124].

Collectively, by secreting a variety of angiogenic factors, CAFs can recruit and activate cells related to angiogenesis, such as endothelial cells and monocytes. These cells then gather and proliferate at the tumor site and form new vascular networks that provide essential nutrients and oxygen that further support tumor growth and metastasis. These studies shown that, by facilitating the formation of new blood vessels in tumors, CAFs enhance the metastatic capability of tumors. Thus, targeting CAFs or their capacity for facilitating angiogenesis may be a therapeutic avenue for intervention in some cancers [125].

The interplay between CAFs and tumor cells

Regulation of metabolism

Recent studies indicate that CAFs are key regulators in modulating tumor cell metabolism, particularly through the regulation of pathways for glucose, amino acid, and lipid metabolism [126, 127] (Fig. 5A). A lipid-rich CAFs subset marked by Abca8a expression has been identified in SETD2-deficient pancreatic tumors through scRNA-seq experiments. Notably, loss of SETD2 activates the BMP2 signaling pathway through ectopic gene expression, thereby promoting the differentiation of lipid-rich CAFs. These ABCA8a-expressing lipid-rich CAFs can promote tumor growth by transfer of lipids and can

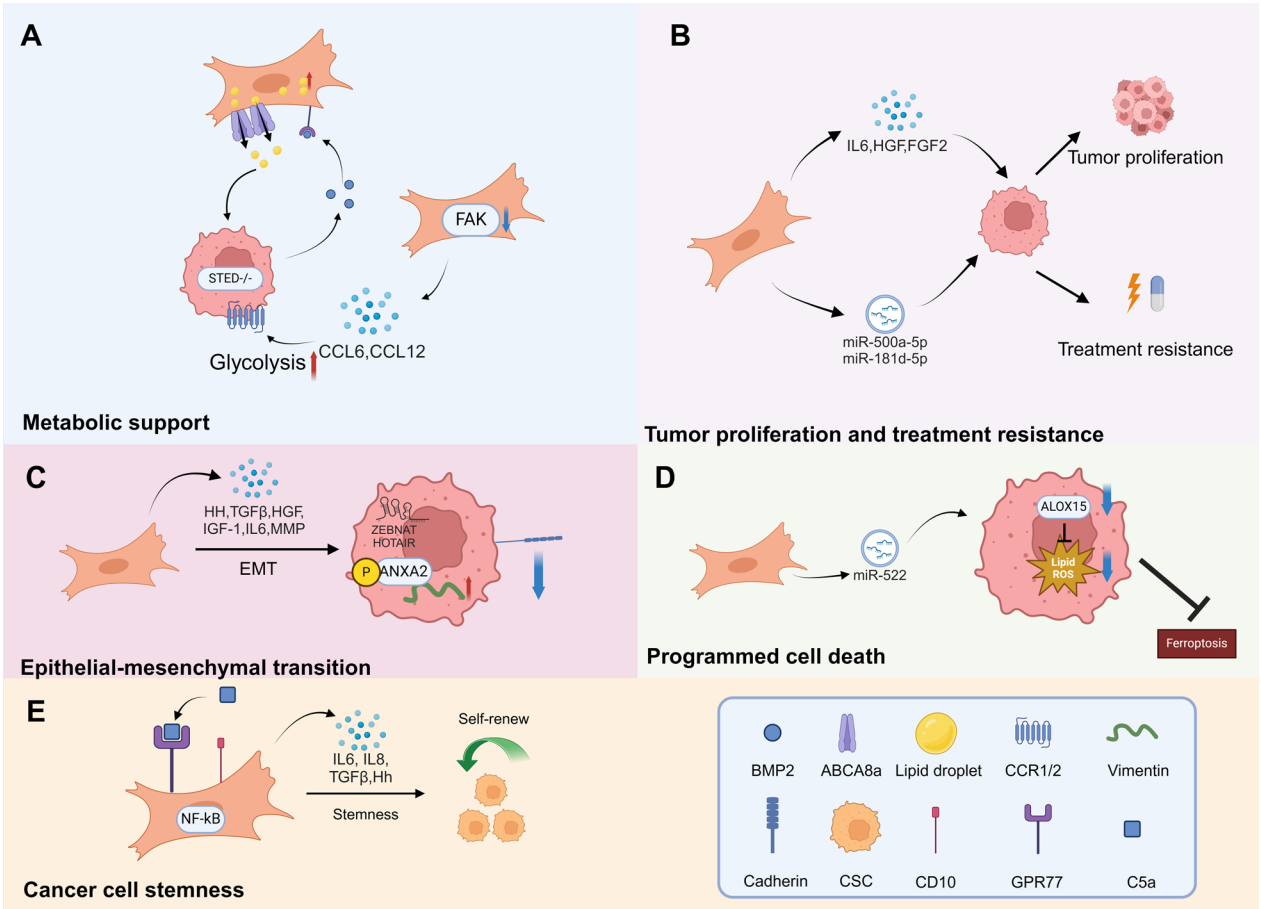


Fig. 5 Interplays between CAFs and tumor cells. (**A**) CAFs fuel tumor cell glycolysis via CCL6 and CCL12 secretion; In addition, Abca8a + CAFs facilitate tumor cell growth by secreting lipid droplets. (**B**) CAFs enhance tumor proliferation and therapy resistance through IL-6, HGF, and FGF2 secretion, and via exosomal long non-coding RNAs (lncRNAs). (**C**) CAFs induce epithelial-mesenchymal transition (EMT) via Hedgehog ligands, TGF-β, and HGF. (**D**) CAF-derived exosomes containing *miR-522* suppress lipid peroxidation to inhibit ferroptosis. (**E**) Complement component 5a (C5a) activates GPR77 + CAFs, inducing tumor stemness via IL-6, IL-8, and TGF-β. This figure was created with BioRender.com

support oxidative phosphorylation by tumor cells [128]. In another example, FSP + CAFs have been shown to increase glycolysis in malignant cells through FAK signaling. Indeed, FAK depletion in CAFs leads to increases in levels of CCL6, CCL11, CCL12 and pentraxin-3, which altogether enhance glycolysis by malignant cells through activating protein kinase A via CCR1/CCR2 [129]. Moreover, secretion of acetate, a metabolic product, by CAFs serves as a critical driver for the accelerated growth of PDAC cells under low pH conditions. Acetate, mediated by acetyl-CoA synthetase 2 (ACSS2), induces acetylation of histones and the oncogenic SAT1 gene, upregulating its expression through epigenetic regulation. It has been shown that knockdown of SAT1 expression levels significantly inhibits PDAC cell growth rates and impairs their survival under low pH conditions. The ACSS2–SP1–SAT1 regulatory axis is a pivotal mechanism by which CAF-derived acetate fuels PDAC cell survival and proliferation, underscoring its potential as a therapeutic target for intervention [130].

CAFs directly promoting tumor growth and treatment resistance

CAFs have been suggeseted to directly promote tumor growth by enhancing cancer cell proliferation and treatment resistance through IL-6 (Fig. 5B). In studies of co-cultures with ductal carcinoma in situ (DCIS) cells, CAFs have been reported to facilitate the formation of multicellular structures via paracrine IL-6 signaling [57]. In the context of esophageal cancer, IL-6 is aberrantly expressed in fibroblasts and epithelial cells, and its levels have been found to increase in co-cultures of cancer cells and CAFs, resulting in tumor progression [88, 131]. In BC, CAFs promote cancer cell proliferation and radioresistance via IL-6 secretion through the STAT3 pathway, and support cancer progression by secreting hepatocyte growth factor (HGF) and FGF2 via paracrine signaling [132–134]. Additionally, in the context of high dose cancer chemotherapy, CAFs have been found to secrete chemokines that mediate treatment resistance and tumor growth, while low-dose metronomic therapy is suppressive for such pro-cancer signaling [135]. Furthermore, exosomes derived from CAFs that contain LncRNAs such as miR-500a-5p and miR-181d-5p have been found to promote tumor growth through epigenetic mechanisms [136, 137]. Co-culture of PDPN + CAFs with cancer cells induced the resistance of such cells to EGFR-TKIs, and this effect was reversed by knockdown of PDPN expression. Accordingly, patients with PDPN + CAFs showed significantly lower response rates to EGFR-TKIs (53% vs. 83%; $P < 0.01$), suggesting that a better understanding of this subtype of CAFs may be key to enhancing the efficacy of EGFR-TKIs in cancer [138]. In squamous cell carcinoma, activation of nuclear receptors (NRs) in CAFs are associated with resistance to chemotherapy. While cisplatin alone showed limited efficacy, combination therapies with NRs antagonists such as LE135 and bicalutamide significantly delayed tumor growth and enhanced treatment efficacy by modulating CAF-driven processes like invasiveness, proliferation, and energy metabolism [139]. Taken together, while these examples show the capacity for CAFs to directly influence tumor growth and treatment resistance, the extent through which CAFs exert such direct effects across cancers remains unclear.

CAFs promote EMT

EMT is an important biological process in which tumor cells transform from epithelial-like cells into mesenchymal-like cells that are associated with specific features including enhanced migration and tissue invasion (Fig. 5C) [58, 140]. Studies of co-cultures of PDAC cells with CAFs have found that such mixtures of these cell types results in a remarkable transcriptional heterogeneity at the single-cell level, yet appears to foster gene expression signatures reminiscent of EMT and progenitor (PRO) phenotypes within PDAC cell lines [141]. CAFs have been reported to promote EMT through cytokines such as Hedgehog ligand, TGFβ, HGF, IL6 and IGF-1 [34, 37, 142, 143]. When co-cultured with CAFs, Panc01 cells exhibit EMT features characterized by their increased invasive ability, expression of Vimentin and decreased expression of E-cadherin, features of which could be blocked by inhibiting Hedgehog signaling. Co-culture with CAFs or addition of CM from CAFs can also promote EMT in BC and bladder cancer [37, 143, 144]. Mechanistically, CAFs induce EMT through the phosphorylation of annexin A2 (ANXA2) mediated by HGF and IGF-1 [145]. Moreover, TGFβ secreted by CAFs have been found to induce EMT through an epigenetic mechanism involving the lncRNA ZEB2NAT and HOTAIR [146, 147]. A recent pan-cancer transcriptomic analysis showed that most THBS family genes are upregulated in cancer tissue samples at advanced stages of disease. Immunohistochemistry and multiplex immunofluorescence experiments have revealed that THBS2 is primarily localized in the regions where CAFs reside, and its expression is higher in patients who are unresponsive to oxaliplatin treatment. Molecular docking and Co-IP experiments confirm that COL8A1 that is secreted by THBS2 + CAFs, interacts with ITGB1 and this, in turn, activates the PI3K-AKT signaling pathway to promote EMT, and leading to oxaliplatin resistance in colorectal cancer. Thus a THBS2 + CAFs-COL8A1-ITGB1 axis might be an important consideration in the development of therapeutic interventions for reversing chemotherapy resistance in this form of cancer [148].

Regulation of programmed cell death by CAFs

Programmed cell death (PCD) is an important cellular mechanism in tumor cell biology, and can significantly influence tumor initiation and progression, as well as enhance or curtical the efficacies of tumor treatments and immunotherapies [149–151]. Studies have demonstrated that CAFs can regulate the levels of ferroptosis by tumor cells through secretion of exosomes containing miR-522. When these CAF-derived exosomes are internalized by tumor cells to deliver miR-522, this results in the post-transcriptional inhibition of expression of ALOX15, a protein involved in lipid peroxidation regulation. Indeed, this reduction of ALOX15 reduces the accumulation of lipid ROS and inhibits the occurrence of ferroptosis [152] (Fig. 5D).

CAFs maintaining cancer stem cell property

CAFs have been reported to modulate the properties of cancer stem cells (CSCs) in scirrhous GC, through the TGFβ signaling pathway (Fig. 5E). In BC, NF-κB activation through GPR77-mediated complement signaling induces a subgroup of CD10 + GPR77 + CAFs, which promote tumor growth and chemoresistance by nurturing CSCs through secretion of IL-6 and IL-8 [153]. Moreover, CM derived from CAFs enhanced the formation of spheroid colonies and upregulated the expression of CSC markers in OCUM-12/SP and OCUM-2MD3/SP cells. The level of phospho-Smad2 was elevated upon co-culturing with CAFs, and the stimulatory effects observed with CAF-derived CM were attenuated by the application of TGFβ inhibitors [154]. In murine models of TNBC, neoplastic cells produce Hedgehog ligands that reprogram CAFs to promote a chemo-resistant, CSC phenotype. This reprogramming involves FGF5 expression and increased production of fibrillar collagen [155]. Together, these lines of evidence indicate that CAFs could directly modulate the features of CSCs so as to influence tumor growth and progression.

Heterogeneity and plasticity of CAFs

In recent years, the emerging data provided by scRNA-seq has facilitated the discovery of an increasing number of subpopulations of CAFs that are deinfed by their diverse features and unique functions. Yet, due to the lack of definitive molecular markers for CAFs, our current understanding of the spectrum of reported subpopulations across different studies remains to be clarified [25]. Table 2 summarizes the features of currently reported CAF subpopulations, as shown.

When considering the expression levels of αSMA and the spatial relationships with tumor cells, two CAFs subsets, myoCAFs and iCAFs, are identified in PDAC. MyoCAFs are located immediately adjacent to neoplastic cells and promote disease progression by producing pro-tumoral cytokines and participate in the formation of desmoplastic stroma. On the other hand, iCAFs are typified by their low expression of αSMA and are located further away from tumor cells and affect the tumor microenvironment by secreting IL-6 and other inflammatory mediators [26]. Moreover, myoCAFs and iCAFs show pleiotropic effects when exposed to certain factors. For example, IL-1 and TGF-β that is secreted from cancer cells have been found to antagonistically regulate the transformation of CAFs subsets in opposing ways. Notably IL-1 activates the JAK/STAT signaling pathway by inducing the expression of leukemia inhibitory factor (LIF), leading to the generation of iCAFs; while TGF-β inhibits the IL-1-induced JAK/STAT signaling pathway by downregulating the expression of IL-1 receptor 1 (IL-1R1), promoting the differentiation of CAFs towards myoCAF subtype [156].

Schwann cells are another source of IL-1α that promote the transformation of myoCAFs into iCAFs [27]. Upon inhibition of the Hedgehog pathway or NF-κb signaling pathway with the IRAK4 inhibitor CA-4948, the composition of CAFs transitions from myoCAFs to iCAFs [28, 29]. In addition, a recent study found that inhibition of TAK1 leads to decreased IL-6 expression in CAFs and increased α-SMA expression, and this promoted the conversion of iCAFs to myoCAFs which was concomitant with enhanced anti-tumor immune responses. This mechanistic switch thus positions TAK1 as a strategic therapeutic target within CAFs that could be explored further to determine the effectiveness of combining TAK1 inhibitors with ICIs in the treatment of PDAC [157]. Furthermore, along with these two subsets, studies using scRNA-seq have led to the identification of another CAF subset that is marked by its expression of MHC class II molecules and costimulatory molecules, which activate T-cells and promote anti-tumor immune responses, and thus named antigen-presenting CAFs (apCAFs) [29, 30, 158, 159].

FAP expression combined with other markers, can identify multiple CAF subtypes that typically exhibit immunosuppressive effects [160–162]. In BC, four CAFs subsets described which were identifiable through their expression of a series markers including FAP, CD29, aSMA, S100-A4/ FSP1, PDGFRb, and CAV1. The subset one (CAF-S1) was characterized by high FAP expression, promoted immunosuppression by secreting CXCL12, attracting CD4 + CD25 + T lymphocytes and retaining them through expression of OX40L, PD-L2, and JAM. Morevoer, CAF-S1 also prolonged T lymphocyte survival and facilitated their differentiating into Tregs, through expression of B7H3, CD73, and DPP4 [163]. Also, a CAFs population

Table 2 The heterogeneity of CAFs

CAFs Subgroups	Cancer Type	Main Findings	Species	Markers	Techniques	Refs
six groups	HCC	POSTN + CAFs associated with T cells exclusion and TAM recruitment	Human and mouse	CD36, POSTN, STMN1, CXC12, MYH11 and SEPT7	scRNA-seq, mIHC	[102]
CCL19 + CAFs	HCC	DKK1 + tumor cells hinder the infiltration of CCL19 + CAFs and plasma cells thus inducing immunosuppressive TME	Human	CCL19, DCN	scRNA-seq, mIHC, spatial transcriptome	[93]
AKAP12 + CAFs	BC	Promoting immunosuppression by M2 polarization through IL-34/CSF1R pathway	Human	AKAP12, αSMA, markers of myoCAFs such as ACTA2, FAP, FN1 and COL1A1	scRNA-seq, CyTOF	[221]
7 Subgroup	Lung cancer	Cluster 1 enriched in tumors, Cluster 6 enriched in non-malignant samples. Cluster 2 shows high myogenesis and angiogenesis activity	Human	COX4I2, FIGF, ACTA2	scRNA-seq	[62]
myCAF, iCAF, apCAF	PDAC	iCAFs: Cytokine-secreting CAF, myCAFs: ECM-producing CAFs, apCAFs: Antigen-presenting CAFs that may inhibit T cell–mediated immune response	Human	iCAFs: PDGFRA, CXCL12, myCAFs: ACTA2, TAGLN, CD74, apCAFs: HLA genes	scRNA-seq	[158]
myCAF, iCAF	PDAC	Hedgehog pathway inhibition drives myCAF to iCAF	Human and mouse	αSMA (myCAFs), PDPN, LY6C (iCAFs)	scRNA-seq	[28]
myCAFs, iCAF, apCAF, proliferating CAF	PDAC	Irak4 inhibition reprograms CAFs towards acute inflammatory phenotype to potentiate immunotherapy	Mouse	Genes signatures of TNF signaling, inflammatory response, and angiogenesis	scRNA-seq	[29]
myCAFs, iCAFs, apCAFs	PDAC	Identification of three distinct CAFs subgroups: iCAFs, myCAFs, and apCAFs. apCAFs express MHC class II and CD74, and can activate CD4 + T cells	Human and mouse	iCAFs: CFD, C3, C7; myCAFs: COL1A1, DCN, VIM, FAP, PDPN; apCAFs: MHCII family	scRNA-seq, Imaging mass cytometry	[30]
myCAFs, iCAFs, meCAFs	PDAC	meCAFs were associated with poor prognosis but better immunotherapy response	Human	myCAFs: COL10A1, POSTN; iCAFs: Complement cascades, cytokine-mediated signaling; meCAFs: PLA2G2A, CRABP2, LDHA, PKM2	scRNA-seq	[79]
myCAFs, iCAFs, apCAFs, MSC-like CAFs	PDAC	Combined MEK and STAT3 inhibition reprograms CAFs to enrich for MSC-like CAFs, attenuating iCAFs and myCAFs, reversing immunotherapy resistance	Mouse	iCAFs: Il6, Cxcl1, Il33; myCAFs: Tgfb1, Acta2, Ccn2, Lrrc15; apCAFs: Cd74; MSC-like CAFs: Ly6a, Cd34, Pdpn, Lslr (Meflin)	CRISPR/Cas9 gene editing, scRNA-seq, CyTOF	[98]
myCAFs, iCAFs, apCAFs, RGS5 + myCAFs	PDAC	Accumulation of RGS5 + myCAFs in liver metastasis associated with poor prognosis	Human	myCAFs: ACTA2, COL3A1; iCAFs: CFD, C3, C7; apCAFs: CLU, C11orf96, MT1M; RGS5 + myCAFs: RGS5, FN1	scRNA-seq, mIHC	[167]
Lipid-laden CAFs	PDAC	ABCA8a + lipid-laden CAFs promote tumor cells growth through fueling OXPHOS by transferring lipid	Human and mouse	ABCA8a	scRNA-seq	[128]

Table 2 (continued)

CAFs Subgroups	Cancer Type	Main Findings	Species	Markers	Techniques	Refs
CD10 + GPR77 + CAFs	BC and Lung Cancer	CD10 + GPR77 + CAFs sustain cancer stemness and promote tumor chemoresistance	Human and mouse	CD10, GPR77	Flow Cytometry, Gene Microarrays, etc	[153]
FAP + CAFs, αSMA + CAFs	PDAC	FAP + CAFs promote PDAC progression; αSMA + CAFs restrain PDAC but confer gemcitabine resistance via IL6 production	Human and mouse	FAP, αSMA	scRNA-seq, mIHC	[166]
CAF-S1, CAF-S2, CAF-S3, CAF-S4	BC	CAF-S1 subset promotes immunosuppression by attracting and retaining CD4 + CD25 + T lymphocytes, enhancing regulatory T cell differentiation and activity	Human	CD29, FAP, FSP1, αSMA, PDGFRβ, CAV1	Flow Cytometry, Immunohistochemistry, etc	[163]

marked by co-expression of FAP + PDPN + is predominantly located at the tumor periphery near T cells and inhibits their proliferation via nitric oxide [164]. Correspondingly, a high ratio of S100A4 + to PDPN + CAFs is predictive of good prognosis across subtypes [165]. In studies of 4T1 and 4T07 orthotopic TNBC models, the heterogeneity of CAFs subsets was found to gradually diminish with toumor progression, with CD26 + CAFs and FAP + CAFs becoming the dominant subsets observed in the latter stages of tumor growth [23]. In PDAC, FAP + CAFs promote the growth of pancreatic cancer tumors through CXCL12 and CCL2 signaling, while αSMA + CAFs mainly inhibit tumor growth and contribute to the polarization of tumor-infiltrating T-cells, as revealed by studies using scRNA-seq [166].

In recent years, the advent of scRNA-seq has led to the identification of an increasing number of CAF subpopulations in cancer. Bartoschek et. al. grouped CAFs from BC mouse models into four subgroups, including vascular CAFs (vCAFs), matrix CAFs (mCAFs), cycling CAFs (cCAFs) and developmental CAFs (dCAFs). In cohorts derived from the TCGA database, the signatures of vCAF and mCAF were both independent prognostic factors for BC patients [24]. Studies of the Panc02 tumor model have found that, gemcitabine chemotherapy upregulates placental growth factor (PlGF), and induces CD141 + CD74- CAFs [86]. In loose-type PDAC, a subgroup of CAFs with a highly activated metabolic state (meCAFs) marked by PLA2G2A and CRABP2 expression was discovered, which increased activity of immune cells [79]. Moreover, a subset of myoCAFs marked by RGS5 + has been found to be crucial to the formation of metastatic lesions, predominantly in hepatic metastasis tissues [167]. Also, a lipid-rich CAFs subpopulation marked by ABCA8a in pancreatic tumors with SETD2 deficiency metabolically supports the growth and survival of tumor cells [128]. In addition, LRRC15 + CAFs, which rely on TGFβ signaling, play a pivotal role in establishing the tumor-fibroblast equilibrium that fosters tumor expansion. Notably, these cells exert a direct inhibitory effect on CD8 + T-cell function, thereby constraining the efficacy of ICB therapies [36]. Neutralization of TGFβ reshaped CAFs subpopulations, with decreased frequency and activity of myoCAFs, while promoting a CD73 + CAF population that exhibited strong response to interferon and enhanced immunomodulatory properties, which improved efficacy of PD-1 immunotherapy [168]. Using multi-omics techniques, two CAF subtypes were identified in prostate cancer regulated by: immunosuppressive ECM-associated CAFs (ECM-CAFs), and lymphocyte-associated CAF (Lym-CAFs) that promoted anti-tumor immunity. YAP1 is a key factor that regulates the transition from Lym-CAF to ECM-CAF phenotype by directly interacting with IKKα to inhibit the activation of NF-κB p65 (also known as RelA). Indeed, selective depletion of YAP1 in ECM-CAFs may be a potential strategy through which to significantly enhance the therapeutic effects of anti-PD-1 antibodies in some cancers [169].

Therapeutic implications of CAFs

Therapies that target CAFs can be categorized into four primary approaches: targeting the ECM generated by CAFs, directly eliminating CAFs marked by their specific gene expression signatures, interrupting the crosstalk between CAFs and the TME, and normalizing CAFs [170–172]. Studies using preclinical models have demonstrated promising anti-tumor effects of CAF-targeted treatments and this has led to clinical studies, however effective treatments remain to be determined through large-scale Phase III clinical trials [98, 168, 173–176]. Strategies to targeting CAFs for cancer therapy are summarized in Tables 3 and 4.

Targeting CAF-derived ECM to treat cancer

HA is a major glycosaminoglycan in PDAC stroma, elevates interstitial fluid pressure and compromises vascular perfusion, limiting chemotherapeutic delivery. PEGPH20 is a pegylated recombinant hyaluronidase enzyme that targets HA. Studies shows PEGPH20 reduces tumor-associated hyaluronan, which can enhance drug delivery, decrease tumor interstitial pressure, and improve vascular permeability [177, 178]. Preclinical and phase I/Ib studies have demonstrated that PEGPH20 in combination with gemcitabine was well-tolerated and may have therapeutic benefits [179]. Although early studies have shown effectiveness, a phase III study (HALO 109–301) found that while the addition of PEGPH20 to nab-paclitaxel/gemcitabine increased the objective response rate (ORR), it did not improve OS or progression free survival (PFS) in patients with hyaluronan-high metastatic PDAC [180–182]. Losartan is a commonly used angiotensin II receptor blocker, originally used to treat high blood pressure by blocking the angiotensin II receptors to dilate blood vessels [183]. More recently, it has been demonstrated to exhibit anti-tumor effects by targeting the tumor stroma, reducing collagen and hyaluronan production, and consequently decreasing solid stress in tumors, which leads to improved vascular perfusion and drug delivery which, in turn, potentiates chemotherapy in BC and PDAC models [184, 185]. Moreover, losartan improves the penetration and effectiveness of nanotherapeutics in desmoplastic tumors by inhibiting collagen production [186]. Additionally, in a single-arm phase 2 clinical trial, it was associated with a high R0 resection

Table 3 Strategies to targete CAFs for cancer therapy

Target	Drugs	Class	Strategy	Mechanism	Cancer models	Refs
FAP	αFAP-Z@FRT, nano-PIT, scFv-Z@FRT, mAb-IR700	FAP-specific single chain variable fragment (scFv)-conjugated photosensitizer	Depletion of CAFs	Targeting FAP + CAFs by photodynamic therapy, eliciting cellular immunity against FAP + CAFs and tumor cells	Breast cancer, ESSC	[234–237]
FAP	αFAP-PE38	FAP-targeting immunotoxin	depletion of FAP + CAFs	Depletion of FAP + CAFs, modulating TIME	Breast cancer	[229]
FAP	PT630	FAP and DPPIV inhibitor	Targeting ECM	FAP activity inhibition	Lung and colon cancers	[77]
FAP	CAP-NPs	Drug-loaded FAP cleavable nanoparticles	Targeting ECM	FAP mediated drug release	Prostate cancer	[230]
FAP	FAPα-Vax	FAP expressing tumor cell vaccine	Depletion of CAFs	Reverse immunosuppressive TME by depletion FAP + CAFs	Breast cancer, CRC	[174, 228]
PDGFR pathway	Imatinib	PDGFR inhibitor	Blocking cross-talk of CAFs and TME	Reducing growth factors and angiogenic factors secreted by CAF	Cervical cancer	[123]
CTGF	FG-3019	anti-CTGF	Blocking cross-talk of CAFs and TME	Enhancing chemotherapy response by downregulation of the X-linked inhibitor of apoptosis protein	PDAC	[81]
Hedgehog pathway	IPI-926	smoothened	Targeting ECM	Enhancing tumor vasculature and perfusion to faciliate drug deliveryinhibition	PDAC	[196]
Sst1 somatostatin receptor	Pasireotide	somatostatin analogue	CAFs normalization	Activating the sst1 receptor on CAFs and reducing synthesis of secreted proteins including IL-6	PDAC	[220]
CXCL12-CXCR4 axis	AMD3100	CXCR4 inhibitor	Blocking cross-talk of CAFs and TME	Blocking the SDF1–CXCR4 ineraction to increase CD8 + T cell infiltration	PDAC	[87]
Vitamin A metabolism	ATRA	Vitamin A analogue	CAFs normalization	Inducing quiescence of PSCs and reducing cancer cell proliferation by recovery of Vitamin A storageand PSC deactivation	PDAC	[243, 245]
Vitamin D receptor	Calcipotriol	vitamin D analogue	CAFs normalization	reprogramming PSCs to the quiescent state and reducing ECM depostionactivation and PSC deactivation	PDAC	[249]
Angiotensin receptor	Losartan-loaded C16-N	peptide hydrogel as a local losartan depot	CAFs normalization	normalizing CAFs through down-regulation of thrombospondin-1, inhibiting TGFβ pathway	Breast cancer	[185]

Table 3 (continued)

Target	Drugs	Class	Strategy	Mechanism	Cancer models	Refs
TGF-β	LY2157299, LY2109761	Inhibitor of TGF-β receptor I	CAFs normalization	Blocks the fibroblast activation induced byTGF-β	Ovary cancer,HCC	[209, 213]
TGF-β	Artesunate (ARS) and dihydroartemisinin (DHA)	Artemisinin derivatives	CAFs normalization	Inactivates CAF and inhibits metastasis	Breast	[172]
TGF-β	Pirfenidone	TGF-β antagonist	CAFs normalization	inhibiting CAF proliferation by induction of apoptosis	Breast	[195]
NAD(P)H Oxidase-4 (NOX4)	GKT137831	NOX4 inhibitor	CAFs normalization	Reverts the myofibroblastic-CAF phenotype and delays tumor growth	Head and neck cancer, colorectal cancer, esophageal adenocarcinoma	[241]
CSF1R + CXCR2	JNJ-40346527 and SB225002	CSF1R inhibitor and CXCR2 inhibitor	Blocking cross-talk of CAFs and TME	Blocks pro-tumoral PMN-MDSC recruitment and reduces tumor growth	Lung, breast, colon, others	[114]
sTRAIL	sTRAIL LPD	plasmids encoding sTRAIL loaded lipid-coated protamine DNA complexes	CAFs normalization	Reverses CAFs to a quiescent state and triggers tumor cell apoptosis	Bladder carcinoma	[242]
integrin αvβ3	ProAgio	Protein targeting integrin αvβ3	Depletion of CAFs	Reduces intratumoral collagen and decreases growth factors released from CAFs by inducing apoptosis in integrin αvβ3–expressing CAFs	TNBC	[225]
Nuclear receptors (NRs)-retinoic acid receptor β and androgen receptor	EB1089 and LE135	Retinoic acid receptor β and androgen receptor antagonists	CAFs normalization	inhibits the pro-cancerous functions of CAFs and reducing chemoresistance	skin SSC	[139]
GPR77	Anti-GPR77 antibody	mAb	Depletion of CAFs	Depletion of GPR77 + CAFs to reverse resistence to chemotherapy and stemness	Breast cancer	[153]
CCR2	sc-202525	CCR2 inhibitor	Blocking cross-talk of CAFs and TME	Reversing recruitment of monocytes and their transformation to MDSCs	Lung cancer	[110]
IL-6	tocilizumab	Anti-IL-6 receptor monoclonal antibody	Blocking cross-talk of CAFs and TME	Reverses inhibition of chemotherapy-induced apoptosis by blocking CAFs derived IL-6	Gastric cancer	[215]
IGF2/IGF1R axis	linsitinib	small molecular inhibitor	Blocking cross-talk of CAFs and TME	Blocking IGFR2 mediated interaction between CAFs and T cells via CXCL12 and PD-L1	Breast cancer, CRC, melanoma	[89]

Table 3 (continued)

Target	Drugs	Class	Strategy	Mechanism	Cancer models	Refs
NAMPT	NAMPT-containing Evs	culture supernatant of mouse BMDM overexpressing Nampt	Blocking cross-talk of CAFs and TME	EVs containing NAMPT restore CD8 + T cell function by inhibiting NNMT expression in CAFs	gastric cancer	[222]
Senescent CAFs	ABT-199(venetoclax)	BCL-2 inhibitor	Depletion of CAFs	Depletion of senescent CAFs to restore CD8 + T cell activity		[238]
IL-34	anti-IL-34	mAb	Blocking cross-talk of CAFs and TME	Inhibiting M2 polarization mediated by AKAP12 + CAFs derived IL-34	breast cancer	[221]

Table 4 Clinical trials evaluating CAFs directed therapies

Target	Drug/Compound	Disease	Combination	Key Results	Trial Phase	Trial Number	Refs
JAK/STAT pathway	Ruxolitinib	PDAC	Placebo + Capecitabine	Well tolerated; may improve survival in patients with inflammation (elevated serum C-reactive protein)	Phase II	NCT01423604	[211]
FGFR	Futibatinib (TAS-120)	BC	Fulvestrant	6-month PFS: 45.5% (95% CI: 24.4, 67.8); Median PFS: 7.2 months (95% CI: 2.1, 7.6)	Phase II	NCT04024436	[218]
PDGFR	Imatinib	Neurofibromas	None	ORR: 17%; Imatinib may be effective for treating plexiform neurofibromas in NF1 patients	Phase II	NCT01673009	[124]
CTGF	S-3304	Solid tumors	None	Well tolerated; satisfactory plasma concentrations	Phase I	NCT00033215	[64]
CTGF	Pamrevlumab (FG-3019)	PDAC	Placebo + Gemcitabine/Nab-Paclitaxel	CA 19–9 response (≥ 50% decline from baseline): 65% (experimental) vs 42% (control); Pamrevlumab may enhance gemcitabine/nab-paclitaxel neoadjuvant therapy	Phase I	NCT02210559	[223]
Hedgehog	IPI-926	PDAC	Cetuximab, Gemcitabine, FOLFIRINOX, None	Well tolerated with signs of antitumor efficacy; High ORR (67%) in advanced pancreatic adenocarcinoma	Phase I, Ib/II, I, I	NCT01255800	[198]
CXCR4	AMD3100 (Plerixafor)	Glioblastoma, PDAC	Bevacizumab, Cemiplimab	Well tolerated; Plerixafor distributes to CSF and brain tumor tissue; ORR: 19% in pancreatic cancer	Phase I, II	NCT01339039, NCT04177810	[214]
CXCR4	Balixafortide	BC	Eribulin	Well tolerated; Promising efficacy with ORR: 33%	Phase I	NCT01837095	[212]
Tenascin	131I-m81C6	Brain tumors	Chemotherapy	Well tolerated; OS greater than historical controls treated with surgery + iodine-125 brachytherapy	Phase II	NCT00003461	[170]
Hyaluronic acid	PEGPH20	PDAC	Nab-Paclitaxel + Gemcitabine, Eribulin, Nab-Paclitaxel + Gemcitabine	Improved PFS in pancreatic cancer (HA-high tumors); 5/14 PR in breast cancer; Increased ORR but no improvement in OS or PFS in pancreatic adenocarcinoma	Phase II, Ib/II, III	NCT01839487, NCT02753595, NCT02715804	[182]
Vitamin D metabolism	Paricalcitol	BC	Chemotherapy	Well-tolerated	Phase I	NCT00637897	[240]
Angiotensin receptor	Losartan	PDAC	Hypofractionated radiation therapy after chemotherapy	No results posted yet	Phase I	NCT04106856	N/A
TGF-β	LY3200882	Solid tumors	Gemcitabine	Safe and well-tolerated; 6/12 PR, 3/12 stable disease; Overall DCR: 75%	Phase I	NCT02937272	[210]
FAP	131I-Sibrotuzumab	FAP + cancer	None	Repeated infusions administered safely	Phase I	NCT02209727	[231]

rate when incorporated into a total neoadjuvant therapy regimen for locally advanced pancreatic cancer [187]. Tranilast is a TGF-β inhibitor, originally approved as an anti-allergic drug used to treat allergic diseases [188]. Tranilast exhibits antitumor effects by normalizing the TME, improving tumor perfusion and oxygenation, and enhancing the efficacy of both nanomedicine and immunotherapy [189, 190]. As a further example, Metformin, a widely used medication primarily prescribed for the treatment of type 2 diabetes, and the anti-fibrotic drug Pirfenidone, have both been found to reduce ECM production by inhibiting the activation of CAFs [191–195].

Hedgehog signal pathway plays a vital role in ECM deposition. In a hypo-perfused gemcitabine-refractory mouse model of PDAC, coadministration of IPI-926, a hedgehog inhibitor, increased tumor vasculature and gemcitabine concentration, leading to temporary disease stabilization [196]. In phase I trials, treatment with IPI-926 showed preliminary efficacy, but this approach failed in a phase II trial [197–200]. Similarly, in phase Ib and phase II trials, another antagonist, vismodegib, also failed to enhance the ORR, PFS or OS in patients with metastatic PDAC in combination with gemcitabine [201, 202]. Lee et al. showed that modulation of Hedgehog pathway disrupts the balance between epithelial and stromal elements, leading to accelerated growth of epithelial cancer cells, which may explain its failure in clinical trials [203].

ROCK, a protein kinase involved in cell migration and ECM synthesis, is overexpressed in pancreatic cancer cells and CAFs, suggesting it may be a therapeutic target [204]. Fasudil is a ROCK inhibitor that is primarily used to treat cerebral vasospasm and has shown potential in various other conditions, including cancer, due to its effects on cell motility and smooth muscle contraction. Inhibition of ROCK with fasudil reduced tumor collagen deposition, enhanced survival, and increased chemotherapy uptake, highlighting the potential of targeting tumor stroma to enhance treatment efficacy in pancreatic cancer [205, 206]. Therefore, targeting ECM produced by CAFs may be a viable approach to cancer, but futher research is necessary to develop their clinical application as an effective treatment option.

Targeting signaling pathways relevant to cross-talk between CAFs and TME

Many growth factors, interleukins, chemokines and other cytokines such as TGFβ, IL1, IL6, CXCL12, CCL6 are involved in signaling cross-talk between CAFs and TME [47, 166, 207–209] (Fig. 6D). Such factors are known to activate various signal pathways including Smad, JAK-STAT, NF-κB among others to induce the expression of downstream genes. Since CAFs and the TME interact through various signaling molecules, specific blockade of their signaling cross-talks likely exerts targeted anti-tumor effects. Through this line of reasoning, many targeted drugs for these signaling pathways have been evaluated in preclinical or clinical studies for such effects [87, 210–213]. Although the initial purpose of developing these drugs may not have been specifically for use to affect CAFs, they can still potentially be repurposed for application due to their ability to interfere CAF signaling [214].

It is known that expression of IL-6 is significantly increased by αSMA + CAFs during gemcitabine treatment. When the IL-6 signaling pathway was blocked, the combined use of gemcitabine and ICB therapies significantly improved the survival of mice with pancreatic cancer [166]. Similarly, IL-6 was found to protect GC cells from 5-fluorouracil-induced apoptosis via the JAK/STAT3 signaling pathway, which is reversed by treatment with the anti-IL6 mAb, tocilizumab [215]. Both pharmacological inhibition of LIF and genetic ablation of Lifr significantly impedes tumor progression and enhances the effectiveness of chemotherapy, thereby prolonging survival in mouse models of PDAC [216]. In another scenario, the Hedgehog signaling pathway is critical to promote CSCs, and therefore blocking this pathway can inhibit tumor growth. Stromal treatment of patient-derived xenografts with smoothened inhibitors (SMOi) effectively downregulates CSC marker expression by inhibiting the Hedgehog signaling pathway, thus sensitizing the tumors to docetaxel treatment. In the phase I clinical trial EDALINE, 3 out of 12 patients with TNBC derived clinical benefit from the combination therapy of the SMOi Sonidegib and docetaxel chemotherapy, with one patient achieving a complete response [155].

CAFs contribute to the development of resistance against HER2-targeted therapies by secretion of FGF5, which triggers the activation of fibroblast growth factor receptor 2 (FGFR2) in adjacent BC cells. The subsequent transactivation of HER2 by FGFR2, mediated through c-Src, ultimately leads to the emergence of resistance to HER2-directed therapeutic interventions [217, 218]. The PI3K-AKT-mTOR pathway mediates the resistance of HER2 + BC to HER2 inhibitors through bypass activation [219]. In PDAC, inhibition of the mTOR pathway with Pasireotide also enhances chemotherapy efficacy by reducing CAFs protein synthesis and tumor growth [220]. Inhibition of CSF1R leads to increased PMN-MDSC. To overcome this unfavorable effect, combination therapy of CSF1R inhibitor and CXCR2 antagonist is reasonable. This strategy not only halts the infiltration of granulocytes into tumors, but also demonstrates potent anti-tumor effects [112–114]. TGF-β1 secreted by CAFs activates Laminin 2 (Ln-2) through the JNK/AP1

signaling pathway thus contributing to immunosuppression. These effects could be blocked by the TGF-β receptor inhibitor galunisertib and a neutralizing antibody against TGF-β1 [47].

Recently, multi-omics analyses have revealed that AKAP12 + CAFs in TNBC secrete IL-34, which binds to CSF1R on macrophages, activating the PI3K/AKT/IL-34 signaling pathway to promote M2 polarization and induce an immunosuppressive tumor microenvironment. This is associated with resistance to PD-1 inhibitors. Blocking the IL-34/CSF1R pathway with an anti-IL-34 antibody is a promising approach to improve the effectiveness of anti-PD-1 therapy in TNBC [221]. Metabolic cross-talk of CAFs and TME is associated with ICIs resistance. Intriguingly, an elevated NAM (nicotinamide)/MNAM (methylnicotinamide) ratio positively correlates with enhanced effector T cell function, while CAFs and macrophages regulate CD8 + T cell function via nicotinamide metabolism, revealing a "face-off" mechanism. CAFs suppress CD8 + T cell cytotoxicity by expressing nicotinamide N-methyltransferase (NNMT) and producing MNAM, which is inhibited by extracellular vesicles (EVs) containing nicotinamide phosphoribosyltransferase (NAMPT) derived from macrophages via NOCTH signaling pathway. Co-administration of NAMPT-containing EVs significantly enhances the therapeutic efficacy of anti-PD-1 therapy in GC. This strategy of modulating NAM metabolism to restore sensitivity to anti-PD-1 treatment demonstrates broad therapeutic potential [222]. In addition, a Phase I/II study showed that adding the anti-CTGF antibody Pamrevlumab to gemcitabine and albumin-bound paclitaxel chemotherapy increased the ORR in unresectable PDAC (65% vs 42%). However, subsequent Phase III clinical trials failed to demonstrate a benefit in OS [223, 224]. Taken together, these examples show potential efficiacy for the use of disruptors of cross-talk signaling between CAFs and TME cells to ameliorate cancer.

Elimination of specific CAF subtypes to treat cancer

A variety of CAF subpopulations marked by candidate gene expression have been shown to promote tumor growth. Thus, the elimination of CAF subtypes via the targeting of their specific markers could be an avenue to treat cancer [225] (Fig. 6C). For example, FAP + CAFs are associated with an immunosuppressive microenvironment, and various therapies targeting FAP have been explored, including monoclonal antibodies, tumor vaccines, radioimmunoconjugates and immunotoxin [226–231]. Tumor cell vaccines or DNA vaccines targeting FAP have been found to enhance the infiltration of CD8 + T lymphocytes and inhibit the accumulation of immunosuppressive cells in the tumor microenvironment. Concurrently, the number of FAP + CAFs within the tumor was significantly reduced [174, 175]. In a C57BL/6 mouse model bearing MCA205 tumors expressing FAP, the radiolabeled drug 177Lu-FAP-2287 rapidly accumulated in MCA205-mFAP tumors, resulting in significant tumor growth inhibition and extended survival time. This treatment also augmented the therapeutic efficacy of anti-PD-1 monoclonal antibodies. 177Lu-FAP-2287 increased the infiltration of CD8 + T cells in the tumor, accompanied by the induction of STING-mediated type I interferon responses and elevated levels of costimulatory molecules such as CD86[173]. FAP-targeted CAR-T cells, followed by CLDN18.2-targeted CAR-T cells, showed enhanced antitumor activity against PDAC by reducing CAFs and MDSCs recruitment, and promoting T-cell survival in the TME. This sequential approach also improve clinical outcomes for PDAC [232]. OMTX705, an antibody–drug conjugate targeting FAP-expressing CAFs, induces tumor shrinkage and regression in NSCLC cancer models in combination with Pembrolizumab [233]. Photodynamic therapy suppressed tumor growth and improved therapeutic outcomes in preclinical models, which selectively eliminates FAP + CAFs by FAP-specific single chain variable fragments (scFv) and ferritin nanoparticles conjugated with photosensitizers [234–237]. Besides, a subgroup of CD10 + GPR77 + CAFs foster tumor growth and chemoresistance, while anti-GPR77 antibodies hinder tumor formation and restore chemosensitivity. Blocking GPR77 with an antibody disrupts the phosphorylation and acetylation of p65, a key component of NF-κB, thereby inhibiting its nuclear accumulation and activity. This leads to reduced secretion of inflammatory cytokines IL-6 and IL-8, chemoresistance, and CSC enrichment [153]. Recently, a subset of senescent CAFs in PDAC has been shown to exhibit increased expression of immune-regulatory genes, contributing to the inhibition of anti-tumor immune responses. Eliminating these senescent CAFs by ABT-199 (venetoclax),a BCL-2 inhibitor, increases activated CD8 + T cells in mouse tumors, while inducing CAF senescence had the opposite effect. Combining ABT-199 with immune checkpoint therapy significantly reduced tumor burden in mice, suggesting that elimination of senescent CAFs through senolytic treatment may be a promising approach to enhance immunotherapy [238, 239].

Normalization of CAFs to treat cancer

An alternative therapeutic strategy targeitng CAFs that is currently explored is to induce the transformation of tumor-promoting CAFs into quiescent fibroblasts, or into CAFs subpopulations that exert tumor-suppressing effects [240–242] (Fig. 6B). All-trans retinoic acid (ATRA), has been shown to reprogram activated PSCs

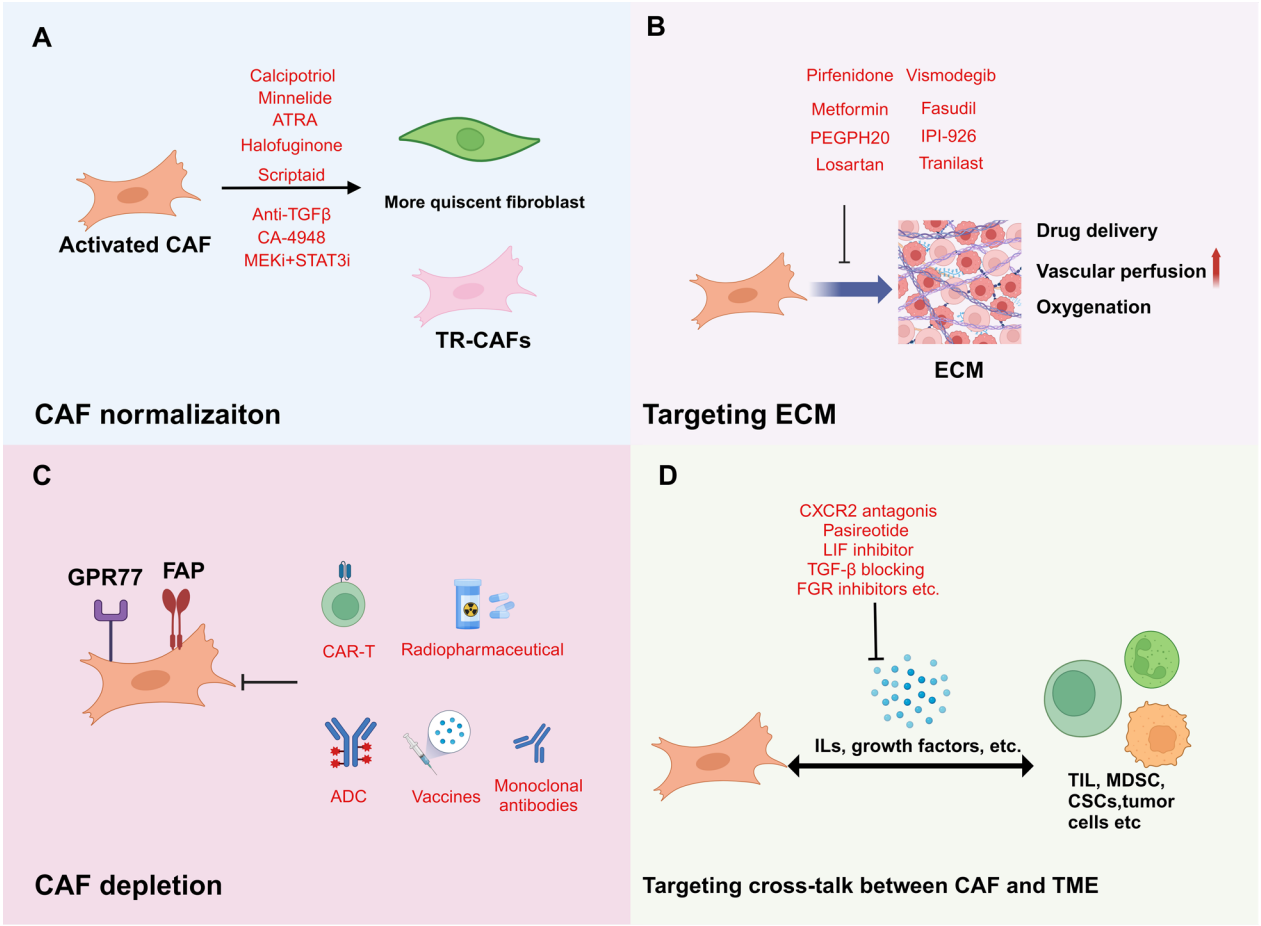


Fig. 6 Therapeutic strategies targeting CAFs. (**A**) CAFs normalization. Treatments such as calcipotriol, ATRA, and minnelide are designed to convert activated CAFs into a more quiescent, normal fibroblast-like state. Another approach includes CAF subpopulations shift from tumor-promoting to tumor-restrain CAFs (TR-CAFs). (**B**) Targeting ECM generated by CAFs. Drugs such as pirfenidone, PEGPH20 and vismodegib modify ECM remodeling process to enhance vascular perfusion and oxygenation within the tumor, thereby facilitating drug delivery. (**C**) Direct depletion of CAFs., strategies utilizing CAR-T cells, radiopharmaceuticals, and monoclonal antibodies (ADCs) have been employed to deplete specific CAFs subgroups through markers such as FAP and GPR77. (**D**) Targeting cross-talk between CAFs and TME. Specific blockade of signal pathway involved in cross-talks between CAFs and TME such as TGF-β, LIF and mTOR, can exert targeted anti-tumor effects. This figure was created with BioRender.com

into a quiescent state [243–245]. Furthermore, a nanosystem has been developed to co-deliver ATRA and siRNA targeting heat shock protein 47 (HSP47) to PSCs, simultaneously inducing quiescence and inhibiting extracellular matrix hyperplasia, which significantly enhances drug delivery and anti-tumour efficacy [246]. Minnelide, a derivative of triptolide reverse the activate CAFs to a quiescent, nonproliferative state [247]. This transformation disrupts the cross-talk between CAFs and tumor epithelial cells, leading to a downregulation of oncogenic signaling. Moreover, Minnelide has been shown to deplete reactive stromal fibroblasts and enhance drug delivery to pancreatic tumors, as evidenced in studies using both patient-derived xenografts and spontaneous pancreatic cancer mouse models [248]. Calcipotriol, a vitamin D receptor (VDR) ligand, effectively reprograms activated CAFs back to a quiescent state in PDAC, improving survival when combined with chemotherapy [249]. Scriptaid, a selective HDACs 1/3/8 inhibitor, reverses CAF differentiation, reducing ECM secretion, cell invasion, and tumor growth in vitro and in vivo, suggesting its potential as an anti-cancer strategy [250].

Treatment with IRAK4 inhibitor CA-494 increases the number of iCAFs with enhanced TNF signaling, inflammatory response, which turns 'cold tumor' refractory to immunotherapy to 'hot tumor' with increased immune cells infiltration [29]. Similarly, neutralizing TGFβ in vivo alters CAFs dynamics, reducing myoCAFs

and promoting iCAFs, which correlates with enhanced anti-tumor immunity and PD-1 immunotherapy efficacy. This mechanism provides a rationale for TGFβ and PD-1 co-blockade in cancer treatment [168]. Fgl2 from tumor stroma accelerates lung cancer progression by activating CAFs and modulating MDSCs in a mouse study, suggesting its role as a therapeutic target [251]. In PKT mice, concurrent inhibition of MEK and STAT3 attenuated the iCAFs phenotype expressing Il6/Cxcl1 and myoCAFs phenotype expressing Lrrc15. While Ly6a/Cd34 + CAFs exhibited mesenchymal stem cell-like characteristics were enriched. The addition of MEKi + STAT3i to PD-1 blockade significantly improves antitumor responses and survival rates in PKT mice. Importantly, this combination achieved clinical benefits in a patient with chemotherapy-refractory metastatic PDAC [98]. The PDGFR inhibitor, Dasatinib, partially reversed the gene expression profile of CAFs, making it more similar to the phenotype of NFs. Specifically, 64 genes that were highly expressed in CAFs were downregulated, 26 genes that were lowly expressed in CAFs were upregulated, and it blocked the tumor-promoting effects of CAF-conditioned medium [252]. Recently, a study suggests that autophagy can promote CAFs into a quiescent state, with reduced secretion of IL-6 and upregulated expression of PD-L1 on tumor cells, thus enhancing the efficacy of ICIs. The combination of anti-PD-L1 and CQ-MSC-Lipo (a biomimetic drug delivery system carrying autophagy inhibitor chloroquine diphosphate) which specifically targets to CAFs effectively suppressed tumor growth [253]. Besides, Mazzeo et al. through ChIP-seq found that androgen receptor negatively regulates ANKRD1, which plays a negative regulatory role in the early stages of CAF activation. Treatment of CAFs with ANKRD1-targeting antisense oligonucleotides (ASOs) led to the simultaneous downregulation of ANKRD1 and key CAFs effector genes such as ACTA2, COL1A1, INHBA, and HAS2. This significantly reduced the proliferation of co-cultured SCC cancer cells, and corresponding in vivo validation was also obtained in mouse models. Therefore, targeting ANKRD1 with ASOs could be a feasible approach to restoring CAF activation and inhibiting tumor progression [254].

Future Perspectives

With the rapid development of cutting-edge technologies such as scRNA-seq, ST, spatial pathology analysis, and organoid models, the complex interactions of CAFs within the TME are gradually being unveiled [82, 89, 93, 157, 221, 255, 256]. These cutting-edge technologies allow for a comprehensive understanding of the diversity of CAFs as well as their functions, both at the single-cell level as well as the spatial levels. The advent of scRNA-seq has revolutionized our understanding of the remarkable heterogeneity, plasticity, and context-dependent roles for CAFs across tumor types. However, while single-cell technologies excel at cataloging cellular diversity, they inherently lack spatial context, and this limitation affects our ability to map CAF interactions within the architectural and functional niches of the TME [257]. One prediction is that emerging technologies that can clarify the spatial pathology of tumors will be an important new frontier for CAF research, and this challenge could be addressed using spatial multi-omics technologies integrated with artificial intelligence-driven tools [258, 259]. As an interesting example, Onder et al. recently revealed the physical connections between multiple TLSs and intratumoral T-cell tracks derived from CCL19 + CAFs in NSCLC. These connections were supported by $CCL19^+$ CAFs that formed a three-dimensional (3D) network spanning tumor tissues which guided T-cell migration via CCL19 chemokine gradients, promoting the distribution and activation of intratumoral T cells. In a murine model, a coronavirus-vectored vaccine (mCOV-Flt3l-gp33) was used to induce $CCL19^+$ CAFs, which increased TLS formation and amplified anti-tumor immunity through interactions with $CD8^+$ T cells. The discovery of this 3D network has provided novel insights into the tumor immune microenvironment, and these findings lay the groundwork for developing fibroblast-based immunotherapeutic strategies in the future [260].

The clinical translation of CAF-related discoveries remains a critical unmet need in oncology. Despite robust preclinical evidence implicating CAF subsets in immune evasion, metabolic symbiosis, and therapeutic resistance, few CAF-targeted therapies have advanced to late-stage clinical trials. Key challenges include the functional plasticity of CAFs (e.g., tumor-restrictive vs. tumor-promoting subsets), biomarker paucity to stratify patients for stromal modulation, and off-target effects of broad stromal depletion. To bridge this gap, interdisciplinary efforts integrating spatial multi-omics, AI-driven digital pathology, and functional organoid models could be mobilized to enhance efforts in this area of exploration. Early successes, such as the development of TAK1 inhibitors to reprogram IL-6-driven CAFs, underscore the potential of mechanistically informed strategies [157]. Concurrently, clinical trials must adopt composite endpoints that evaluate both stromal reprogramming (e.g., ECM normalization, immune infiltration) and traditional oncologic outcomes. By prioritizing translational pipelines that reconcile CAFs heterogeneity with patient-specific TME dynamics, we can unlock the potential for CAFs-targeted therapies to be developed as next-generation combination regimens that are effective for cancer.

Conclusions

CAFs have emerged as pivotal players in the TME, exerting multifaceted influences on tumor progression, immune modulation, angiogenesis, and therapeutic response. In this review, we have showcased the most recent advances regarding the roles of CAFs in cancer development, as well as therapies that target CAFs. Indeed, therapeutic targeting of CAFs encompasses multiple approaches, including targeting the ECM generated by CAFs, directly eliminating CAF subtypes identified by their expression of key markers, interrupting the cross-talk between CAFs and the TME, and through the normalization of CAFs. While preclinical models have demonstrated promising anti-tumor effects of CAF-targeted treatments, large-scale Phase III clinical trials are still needed to validate these findings.

While this review comprehensively synthesizes the current understanding of CAFs in cancer biology, several limitations warrant acknowledgment by the field, such as the current lack of reliable, universal markers to define CAF subsets, discrepancies in findings and tumor progression between animal models and human tumors, technological gaps, as well as interpretation of preclinical observations [25, 89, 257]. The ability to effectively address such limitations requires interdisciplinary collaboration, leveraging advanced spatial technologies, functional genomics, and biomarker-driven clinical trials. Nevertheless, this review demonstrates that CAFs are an important therapeutic target in cancer treatment. A deeper understanding of their roles and their signaling mechanisms in cancer will facilitate the development of more effective and targeted therapies that exploit CAFs, and move this field of research closer towards the promise of novel cancer treatments.

Abbreviations

Abca8a	ATP-binding cassette subfamily A member 8a
ACTA2	Actin alpha 2, smooth muscle
ADFs	Adipose-derived fibroblasts
AKAP12	A-kinase anchor protein 12
AKT	Protein kinase B
ALOX15	Arachidonate 15-lipoxygenase
ANG-2	Angiopoietin-2
ANKRD1	Ankyrin repeat domain 1
ANXA2	Annexin A2
apCAFs	Antigen-presenting cancer-associated fibroblasts
ASOs	Antisense oligonucleotides
ATRA	All-trans retinoic acid
B7H3	B7 homolog 3
BC	Breast cancer
BMP2	Bone morphogenetic protein 2
CAFs	Cancer-associated fibroblasts
cCAFs	Cycling cancer-associated fibroblasts
CCL19	C–C motif chemokine ligand 19
CHI3L1	Chitinase-3-like protein 1
CLCF1	Cardiotrophin-like cytokine factor 1
CLIC1	Chloride intracellular channel 1
CM	Conditioned medium
COL10A1	Collagen type X alpha 1 chain
COL11A1	Collagen type XI alpha 1 chain
COL14A1	Collagen type XIV alpha 1 chain
COL4A1	Collagen type IV alpha 1 chain
CRABP2	Cellular retinoic acid-binding protein 2
CRC	Colorectal cancer
CSCs	Cancer stem cells
CSF1	Colony-stimulating factor 1
CXCL12	C-X-C motif chemokine ligand 12
CXCL3	C-X-C motif chemokine ligand 3
CXCL9	C-X-C motif chemokine ligand 9
CXCR4	C-X-C chemokine receptor type 4
dCAFs	Developmental cancer-associated fibroblasts
DCIS	Ductal carcinoma in situ
DKK1	Dickkopf-related protein 1
DPP4	Dipeptidyl peptidase-4
ECM	Extracellular matrix
ECM-CAFs	Extracellular matrix-associated cancer-associated fibroblasts
EPC	Endothelial progenitor cell
ERK	Extracellular signal-regulated kinase
EVs	Extracellular vesicles
FAK	Focal adhesion kinase
FAP	Fibroblast activation protein
FGF2	Fibroblast growth factor 2
Foxp3	Forkhead box protein P3
FSP1	Fibroblast-specific protein 1
GC	Gastric cancer
G-CSF	Granulocyte colony-stimulating factor
GEMMs	Genetically engineered mouse models
GM-CSF	Granulocyte–macrophage colony-stimulating factor
GP130-IL6ST	Glycoprotein 130-Interleukin 6 signal transducer
GPR77	G protein-coupled receptor 77
GTPase	Guanosine triphosphatase
HCC	Hepatocellular carcinoma
HDAC2	Histone deacetylase 2
HER2	Human epidermal growth factor receptor 2
HGF	Hepatocyte growth factor
iCAFs	Inflammatory cancer-associated fibroblasts
ICC	Intrahepatic cholangiocarcinoma
IGF-1	Insulin-like growth factor 1
IL-1	Interleukin-1
IL-33	Interleukin-33
IL-6	Interleukin-6
IRAK4	Interleukin-1 receptor-associated kinase 4
ITGA11	Integrin subunit alpha 11
ITGB1	Integrin subunit beta 1
JAK	Janus kinase
JAM	Junctional adhesion molecule
KPC	Kras; Trp53; Pdx-Cre (pancreatic cancer model)
Lepr	Leptin receptor
LIF	Leukemia inhibitory factor
LncRNAs	Long non-coding RNAs
LOXL2	Lysyl oxidase-like 2
LRRC15	Leucine-rich repeat-containing protein 15
Lym-CAFs	Lymphoid cancer-associated fibroblasts
mCAFs	Matrix cancer-associated fibroblasts
MCAM	Melanoma cell adhesion molecule
meCAFs	Metabolic cancer-associated fibroblasts
MEF2C	Myocyte enhancer factor 2C
MMPs	Matrix metalloproteinases
MNAM	Methylnicotinamide
MYH11	Myosin heavy chain 11
myoCAFs	Myofibroblastic cancer-associated fibroblasts
NAM	Nicotinamide
NAMPT	Nicotinamide phosphoribosyltransferase
NETs	Neutrophil extracellular traps
NFs	Normal fibroblasts
NF-κB	Nuclear factor kappa-light-chain-enhancer of activated B cells
NNMT	Nicotinamide N-methyltransferase
NSCLC	Non-small cell lung cancer
ORR	Objective response rate
OS	Overall survival

OX40L	OX40 ligand
PD-1/PD-L1	Programmed cell death protein 1/Programmed death-ligand 1
PDGF-C	Platelet-derived growth factor C
PDGFR	Platelet-derived growth factor receptor
PDPN	Podoplanin
PFS	Progression-free survival
PGF	Placental growth factor
PI3K	Phosphoinositide 3-kinase
PLA2G2A	Phospholipase A2 group IIA
PlGF	Placental growth factor
PMN-MDSCs	Polymorphonuclear myeloid-derived suppressor cells
RhoGAP	Rho GTPase-activating protein
RGS5	Regulator of G-protein signaling 5
ROCK	Rho-associated protein kinase
ROS	Reactive oxygen species
SAM	S-adenosylmethionine
scRNA-seq	Single-cell RNA sequencing
SETD2	SET domain containing 2, histone lysine methyltransferase
SPP1	Secreted Phosphoprotein 1(also named Osteopontin)
SR-A/CD204	Scavenger receptor A/CD204
ST	Spatial transcriptomics
STAT3	Signal transducer and activator of transcription 3
TAK1	Transforming growth factor-beta-activated kinase 1
TAZ	Transcriptional co-activator with PDZ-binding motif
TGF-β	Transforming growth factor-beta
THBS2	Thrombospondin 2
TLSs	Tertiary lymphoid structures
TME	Tumor microenvironment
vCAFs	Vascular cancer-associated fibroblasts
VDR	Vitamin D receptor
VEGFA	Vascular endothelial growth factor A
WNT2	Wnt family member 2
YAP1	Yes-associated protein 1
α-SMA	Alpha-smooth muscle actin

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Declarations

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Competing interests
The authors declare no competing interests.

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