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Cancer-associated fibroblasts in the tumor microenvironment: heterogeneity, crosstalk mechanisms, and therapeutic implications

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Abstract

The tumor microenvironment (TME) is increasingly recognized as a critical modulator of the initiation, progression, metastasis, and therapeutic resistance of various cancers. Cancer-associated fibroblasts (CAFs), the predominant stromal cell population within the TME, play pivotal roles in these processes through their remarkable phenotypic and functional heterogeneity. Emerging evidence underscores the diversity in the origins, phenotypes, and functions of CAFs, highlighting their ability to adaptively influence tumor biology in a context-dependent manner. CAFs facilitate cancer malignancy via multiple interconnected mechanisms, including the secretion of soluble bioactive factors, the release of exosomes, the metabolic reprogramming of tumor cells, the remodeling of the extracellular matrix (ECM), and the modulation of the immune microenvironment. CAFs have emerged as attractive and viable therapeutic targets. Recent efforts have focused on developing therapies that disrupt the protumorigenic activities of CAFs or reprogram them toward tumor-suppressive phenotypes. Several of these strategies have shown promise and are advancing into clinical trials. In this review, we comprehensively discuss recent advancements in our understanding of the heterogeneity of CAFs, elucidate their multifaceted interactions within the TME, and explore novel therapeutic strategies targeting CAFs across various cancer types. Our review aims to foster the translation of preclinical insights into clinically effective interventions targeting CAFs.

Keywords Cancer-associated fibroblasts, Tumor microenvironment, Targeted therapy, Crosstalk

Introduction

The tumor microenvironment (TME) is a complex ecosystem surrounding malignant cells, and is composed of diverse cellular and noncellular components, including blood and lymphatic vessels, the extracellular matrix (ECM), signaling molecules, and nonmalignant cells such as immune cells and stromal cells. Accumulating evidence indicates that tumor progression, metastasis, and therapeutic responses are governed significantly by the TME, in addition to tumor-intrinsic genetic alterations [1, 2].

Within this intricate ecosystem, fibroblasts constitute the numerically dominant stromal population [3].

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Cancer-associated fibroblasts (CAFs) were initially identified as activated fibroblasts within or adjacent to tumors, and were characterized by a wound-healing, myofibroblastic phenotype [4–6]. Subsequent studies have revealed that CAFs are phenotypically, functionally, and spatially heterogeneous and capable of promoting malignant proliferation, immune evasion, ECM remodeling, and therapeutic resistance. Moreover, certain subsets of CAFs can suppress tumor growth [7, 8]. This duality makes CAFs both attractive and challenging targets, highlighting the need for precise characterization.

Recent advancements have significantly enhanced our understanding of the biology of CAFs. Single-cell RNA sequencing (scRNA-seq) and spatial transcriptomics have revealed distinct subpopulations and activation states of CAFs and their spatial organization within the TME [9, 10]. Additionally, single-cell proteomics methods such as mass cytometry and imaging mass cytometry have emerged, capturing the phenotypic diversity of CAFs with preserved tissue architecture [11]. In parallel, advanced in vitro models, including patient-derived organoids and composite organoids that integrate multiple stromal components, offer accurate mimics of the native TME [12, 13]. Bioengineering approaches such as 3D bioprinting [14] and microfluidic tumor-on-a-chip platforms [15, 16]enable precise spatial organization and biomechanical control, effectively simulating complex tumor-stromal interactions. Collectively, these innovative techniques provide powerful tools for dissecting the biology of CAFs, elucidating their multifaceted roles within tumors, and paving the way for targeted therapeutic interventions.

While several excellent reviews on CAFs exist, this article places particular emphasis on the spatial niches of CAFs, their functional crosstalk with the TME, and the latest therapeutic strategies under clinical evaluation. In this review, we combine recent research progress to (i) summarize current insights into the origins, activation mechanisms, and heterogeneity of CAFs; (ii) elucidate the reciprocal interactions of CAFs within the TME, including those involving tumor cells, immune infiltrates, other stromal components, and the ECM; and (iii) outline innovative therapeutic strategies targeting CAFs, along with their clinical trial status.

Biological characteristics of CAFs (Fig. 1)

Origins of CAFs

CAFs arise from multiple cellular origins, as under specific stimuli, various cell types can differentiate or transdifferentiate into CAFs. Here, we will discuss several of these origins.

Local fibroblasts and quiescent stellate cells

The most straightforward source of CAFs is local fibroblasts or quiescent stromal cells found in tissue. Normal fibroblasts can transdifferentiate into CAFs upon activation [17, 18]. In pancreatic cancer, CAFs are traditionally derived from pancreatic stellate cells [19, 20], whereas in liver cancer, CAFs originate from hepatic stellate cells [21]. Growth factors, cytokines, and microRNAs secreted by tumor cells activate these stellate cells, leading them to acquire a myofibroblastic phenotype and express transcriptional features unique to CAFs [22, 23]. However, recent lineage tracing studies in pancreatic ductal adenocarcinoma (PDAC) have indicated that stellate cells contribute only a small number of CAFs, suggesting that additional sources also contribute to the overall pool [24].

Transdifferentiation of nonfibroblast lineage cells

Nonfibroblast lineage cells such as epithelial and endothelial cells can transdifferentiate into CAFs through epithelial/endothelial–mesenchymal transition (EMT/EndMT) [25–27]. Although the proportion of CAFs derived from EMT/EndMT remains unclear, these pathways offer direct evidence for the diverse origins of CAFs. Additionally, there are other less common sources of CAFs, including pericytes [28], adipocytes [29], mesothelial cells [30], and smooth muscle cells [31]. For example, adipose-derived stem cells can differentiate into CAFs through Wnt/β-catenin signaling [29] and platelet-derived growth factor (PDGF) and platelet-derived growth factor receptor (PDGFR) signaling [28].

Bone marrow-derived cells

Beyond local sources, bone marrow-derived cells also contribute to the pool of CAFs. Lineage tracing studies in both mouse and human tumors (e.g., colorectal adenoma, gastric cancer, liver cancer, PDAC, and breast cancer) have shown that bone marrow-derived cells can migrate into tumors and differentiate into CAFs [32–36]. For example, bone marrow–derived mesenchymal stem cells (MSCs) can be recruited to tumors via transforming growth factor-β (TGF-β), Wnt, and interleukin-6 (IL-6)/signal transducer and activator of transcription 3(STAT3) signaling and subsequently differentiate into CAFs [37]. In addition, bone marrow monocytes/macrophages may undergo macrophage-to-myofibroblast transition (MMT) under the influence of TGF-β/Smad3 in mouse models, resulting in the loss of typical macrophage markers and the expression of fibroblast markers such as α-smooth muscle actin (αSMA), thereby becoming CAFs [38, 39].

CAFs can originate from local mesenchymal cells, including fibroblasts and stellate cells, transdifferentiated epithelial/endothelial cells via EMT/EndMT, and bone marrow-derived MSCs or monocytes/macrophages. A

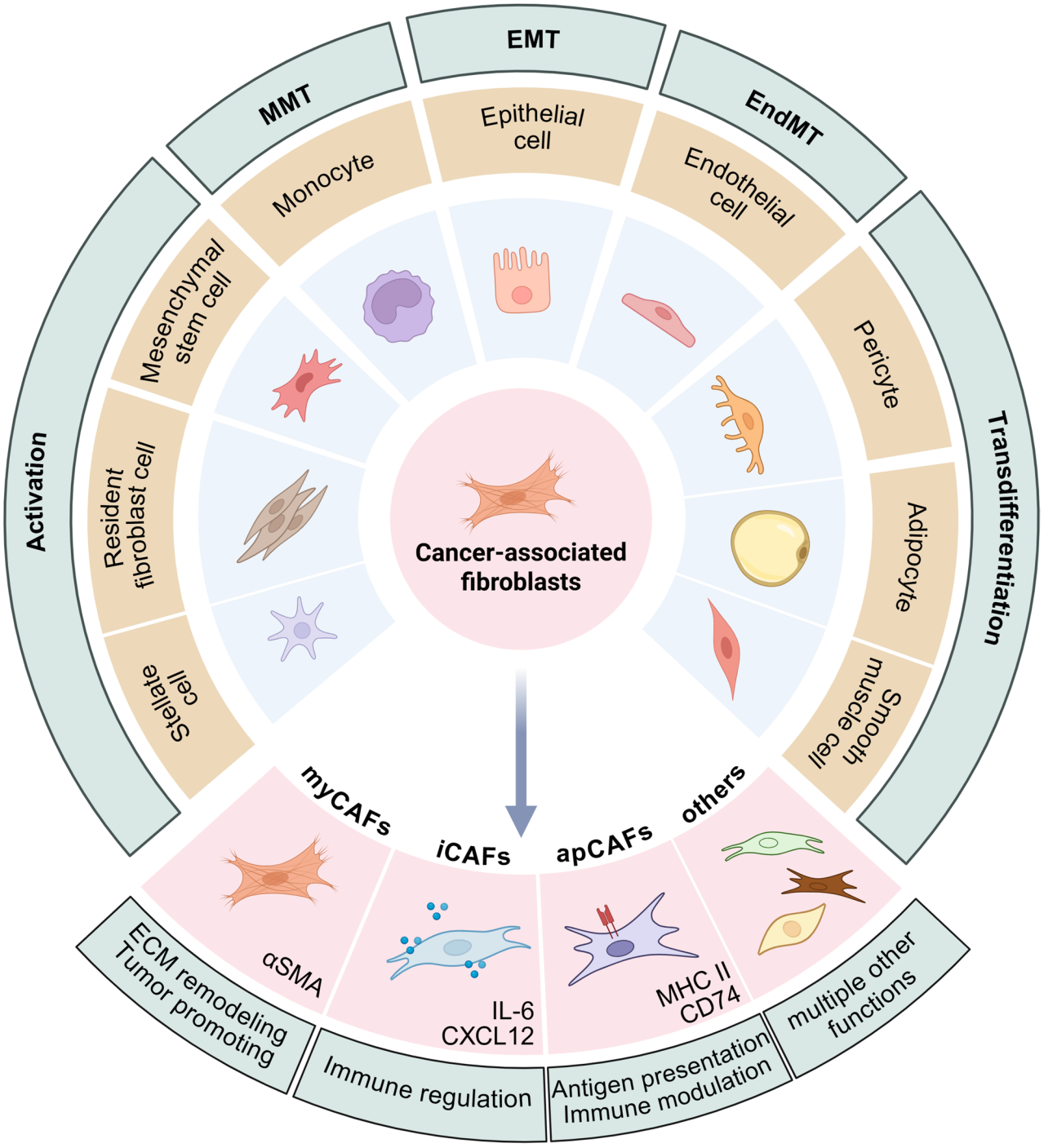

Fig. 1 Heterogeneity in cancer-associated fibroblasts. CAFs exhibit diverse cellular origins. CAFs originate from activation of stellate cells, resident fibroblasts, and MSCs. They also arise through lineage transitions such as monocyte-derived MMT, EMT from epithelial cells, EndMT from endothelial cells, as well as transdifferentiation of adipocytes, pericytes, and smooth muscle cells. CAFs demonstrate considerable phenotypic heterogeneity, distinguishable by specific molecular markers and functional characteristics. Classically, CAFs expressing αSMA are classified as myCAFs. MyCAFs are implicated primarily in ECM remodeling and tumor promotion. iCAFs are characterized by elevated secretion of cytokines and chemokines, which play pivotal roles in immune regulation. apCAFs, identified by their expression of major MHC class II molecules and CD74, are involved in antigen presentation and modulation of immune responses. CAFs, Cancer-associated fibroblasts; MSCs, mesenchymal stem cells; MMT, macrophage-to-myofibroblast transition; EMT, epithelial-to-mesenchymal transition; EndMT, endothelial-to-mesenchymal transition; αSMA, α-smooth muscle actin; myCAFs, myofibroblastic CAFs; ECM, extracellular matrix; iCAFs, Inflammatory CAFs; apCAFs, Antigen-presenting CAFs; MHC, major histocompatibility complex. Original figure created with BioRender.com

variety of factors released by tumors, which will be discussed below, drive the conversion of these cells into CAFs, laying the foundation for their phenotypic and functional heterogeneity.

Activation of CAFs

Before precursor cells can become functional CAFs, they must be "activated" in the TME [40]. Activation refers to the process whereby quiescent or resident cells, upon stimulation by tumor or stroma derived signals, undergo changes in proliferation, migration, secretion, and contractility, similar to activated fibroblasts during wound healing [4–6]. The major mechanisms and pathways include the following:

TGF-β pathway

TGF-β is considered one of the central regulators of the activation of CAFs [41, 42]. TGF-β signaling increases the expression of αSMA and the secretion of ECM components and protumorigenic factors [43]. Through the activation of downstream SMAD signaling, TGF-β induces CAFs to produce connective tissue growth factor (CTGF), collagen type I (COL1A1), and other ECM proteins. Importantly, TGF-β is not only required for the formation of CAFs but also for the maintenance of their activated state [44, 45]. A recent study [46] revealed that in oral squamous cell carcinoma (OSCC), growth differentiation factor 15 (GDF15), a member of the TGF-β superfamily, functions similarly to TGF-β. Specifically, OSCC cells secrete GDF15, which activates the ERK1/2 signaling pathway and induces normal bone marrow MSCs or oral lamina propria fibroblasts to upregulate the expression of markers of CAFs, such as αSMA and vascular endothelial growth factor (VEGF), thereby enhancing their tumor-promoting activity. Conversely, knockdown of GDF15 reversed this observed transformation of CAFs and inhibited tumor cell migration and invasion. Interestingly, different levels of TGF-β may drive subtype switching in CAFs [47]. For instance, high TGF-β activity tends to shift inflammatory CAFs into a myofibroblastic phenotype, denoted myCAFs, highlighting the plasticity of CAFs [45].

Platelet-Derived Growth Factor (PDGF) pathway

In tumors, PDGF ligands (such as PDGF-AA and PDGF-BB) are secreted by cancer cells and tumor-associated platelets, which then activate the receptors PDGFRα/β on the surface of CAFs [48]. PDGF-PDGFR signaling promotes the proliferation, survival, and migration of CAFs to tumor sites while also stimulating the synthesis of ECM components and collagen deposition [44, 49]. Studies have shown that normal fibroblasts, when exposed to PDGF and TGF-β, can undergo phenotypic conversion to become CAFs [50]. It has been reported that PDGF-BB secreted by cancer cells undergoing EMT enhances the matrix-remodeling ability of CAFs [51]. Thus, PDGF signaling is recognized as a key driver of both the activation and function of CAFs.

Proinflammatory cytokines such as IL-1, TNFα and IL-6

Tumor cells and infiltrating immune cells frequently secrete interleukin-1α/β (IL-1α/β) and tumor necrosis factor α (TNFα), which stimulate nearby stromal cells to transition into an inflammatory phenotype, denoted iCAFs [52, 53]. For instance, studies by Öhlund et al. in PDAC revealed two subtypes of CAFs in which the formation of iCAFs depended on the secretion of IL-1α and TNFα by tumor cells [20]. These proinflammatory cytokines activate transcription factors, including nuclear factor κB (NF-κB) and STAT, leading to abundant secretion of additional inflammatory mediators by CAFs. In turn, this promotes the recruitment and regulation of immune cells, further influencing tumor development and progression [54–57]. Similarly, IL-6 released by tumor cells has been shown across multiple cancer types to activate fibroblasts into a protumorigenic phenotype that promotes EMT and tumor invasion [58–61].

Autocrine loop

Once activated, many CAFs establish autocrine feedback loops [62]. A classic example is the IL-6/STAT3 pathway, in which IL-1–stimulated CAFs secrete large amounts of IL-6, which activates STAT3 signaling in the CAFs themselves and neighboring CAFs to maintain an inflammatory secretory phenotype [63]. This autocrine mechanism ensures that CAFs remain activated even when the original tumor signals decline [42]. In addition to IL-6, CAFs may use autocrine signaling through TGF-β to maintain the myofibroblastic phenotype, creating a self-perpetuating environment [42, 64].

In addition to the mechanisms already discussed, various other developmental and stress-related signals contribute to the activation and functional maintenance of CAFs. For instance, under hypoxic conditions, fibroblasts develop an inflammatory gene expression signature. In synergy with cancer cell-derived cytokines, this process promotes the emergence of iCAFs through a mechanism dependent on hypoxia inducible factor 1 alpha (HIF1α) [65]. Similarly, the Hedgehog signaling pathway is involved in maintaining phenotypes and mediating subtype transitions. In CAFs. The inhibition of this pathway decreases the number of myCAFs while increasing the number of iCAFs [66]. Recent evidence also indicates that the Hippo pathway, particularly via yes-associated protein 1 (YAP1), plays a critical role in preserving the ECM-CAFs phenotype and preventing its conversion into the lymphocyte-associated CAFs subtype [67]. Epigenetic regulation further supports the maintenance of

CAFs with specific phenotypes and functions [68, 69]. Additionally, exosomes released by tumor or stromal cells deliver active growth factors, cytokines, and both coding and noncoding RNAs that induce the activation and differentiation of CAFs [70–72]. Oxidative stress also promotes myofibroblast differentiation and tumor metastasis [73]. Collectively, these diverse signals interact with classic tumor-derived factors such as TGF-β, PDGF, IL-1, and fibroblast growth factor (FGF), establishing a complex network of autocrine and paracrine loops that ensures the persistent activation and functionality of CAFs in the TME.

Phenotypic, functional, and spatial heterogeneity of CAFs

Phenotypic heterogeneity

Single-cell and spatial omics analyses have revealed that CAFs do not form a monolithic population but instead exhibit reproducible phenotypes that have been observed across tumor types. Integrative pancancer atlases, constructed from dozens to hundreds of specimens, consistently classify CAFs into three main subtypes.

Myofibroblastic CAFs (myCAFs). One major subtype of CAFs is myCAFs, characterized by matrix production. myCAFs typically localize adjacent to tumor cells and highly express αSMA [74]. These cells are activated by TGF-β signaling and secrete large amounts of extracellular matrix, including collagens, fibronectin and hyaluronan, which increases tissue stiffness and interstitial pressure. Functionally, myCAFs can support tumor growth by remodeling the extracellular matrix and promoting angiogenesis. myCAFs represent a prototypical activated fibroblast subtype that supports the fibrotic, protumorigenic niche in many solid tumors [75].

Inflammatory CAFs (iCAFs). In contrast, iCAFs are a phenotypically distinct subtype characterized by low αSMA expression and high secretion of cytokines and chemokines. iCAFs tend to reside more distally to cancer cells and exhibit upregulation of immunomodulatory factors such as IL-6, IL-11, and CXC motif chemokine 12 (CXCL12) [74]. Functionally, iCAFs orchestrate chronic inflammation and immunosuppression in the TME. They produce large amounts of chemokines and complement components that recruit protumor immune cells and foster an immunosuppressive environment [75].

Antigen-presenting CAFs (apCAFs). Antigen-presenting CAFs are a more specialized subtype. apCAFs were first identified in pancreatic cancer tissues as a small number of CAFs expressing major histocompatibility complex (MHC) class II genes and cluster of differentiation 74 (CD74) but notably lacking costimulatory molecules [74]. While first described in the context of PDAC, similar MHCII$^+$ fibroblasts have since been observed in breast tumors and other cancer types. Through their incomplete antigen-presenting machinery, apCAFs can directly interact with immune cells, resulting in an immune-interacting phenotype that can modulate tumor immune surveillance.

CAFs are highly heterogeneous, and some unique subtypes have been found in different cancers. For example, FAPα$^+$ CD144$^+$ endothelial-like CAFs (endoCAFs), which exhibit a hybrid phenotype of CAFs and endothelial cells, were discovered in PDAC tissue and can promote metastasis [76]. Ye et al. identified a subset of myCAFs that are senescent (senCAFs) in mouse and human breast tumors. ECM secreted by senCAFs specifically limits natural killer cell cytotoxicity [77]. Glycolytic CAFs in soft tissue sarcomas rely on glucose transporter 1 (GLUT1)-dependent expression of CXCL16 to impede cytotoxic T-cell infiltration [78].

Functional heterogeneity

CAFs perform a broad range of functions, which can be remarkably diverse and occasionally opposing. On the one hand, abundant evidence has shown that they (i) sustain malignant cell proliferation and invasion; (ii) stimulate angiogenesis; (iii) shape an immunosuppressive microenvironment; and (iv) foster resistance to therapy [65, 79]. The molecular underpinnings of these protumor functions are detailed in the following sections.

On the other hand, multiple lines of evidence demonstrate that CAFs can also constrain tumor progression [7, 8]. A seminal study from the Kalluri team revealed that genetic depletion of αSMA + CAFs in PDAC reduces stromal fibrosis while decreasing survival, indicating that not all CAFs activities are deleterious [80]. Consistent with these findings, CAFs with specific phenotypes have been correlated with favorable clinical outcomes in some cancers [81, 82]. Mechanistically, dense collagen derived from myCAFs can form a mechanical "cage" that limits tumor cell dissemination [7], and Rhim et al. reported that CAFs can restrain PDAC by reducing fibrosis and hypoxia [8]. Advances in research have refined the classification of CAFs, revealing diverse subtypes with functionally distinct roles.

Beyond these phenotypic and functional layers, CAFs exhibit spatial heterogeneity.

Spatial heterogeneity

Spatial localization is a crucial third dimension in heterogeneity of CAFs, with CAFs detected in spatially conserved niches alongside tumor, immune, and vascular cells and significantly influencing cancer progression and therapeutic responses. On the basis of an integrative analysis of a pancancer spatial multiomics atlas and organ-specific studies [83], on the basis of their niche, CAFs can be categorized into four distinct spatial subtypes (Table 1): barrier/peritumoral, stromal/ECM, myeloid-rich, and tertiary lymphoid structure (TLS)-associated

Table 1 Spatial niches of CAFs: representative markers, neighboring cells/structures, and clinical implications

CAFs Spatial Niche	Representative Markers	Neighboring Cells/Structures	Prognosis/Immunotherapy Response
Barrier/Peritumoral CAFs	COL1A1, ACTA2, CXCL8, TGFB1	Exhausted $CD8^+$ T cells, $CD4^+$ Tregs; adjacent to tumor margins	Form an immune-excluding barrier; associated with poor prognosis
Stromal/ECM CAFs	FAP, PDPN, MMP2	Other stromal cells and vasculature	Promote an immunosuppressive TME and contribute to therapy resistance
Myeloid-rich CAFs	PDGFRB, CCL14	M2-polarized macrophages and neutrophils	Contribute to immune suppression and tumor progression
TLS-associated CAFs	CD74, HLA-DR, CXCL9, CCL19	Naïve T cells, B cells; within the tertiary lymphoid structures	Correlate with better prognosis and improved response to immunotherapy

Abbreviations: *CAFs* Cancer-associated fibroblasts, *COL1A1* collagen type I alpha 1 chain, *ACTA2* Smooth muscle aortic alpha-actin, *CXCL8* CXC motif chemokine ligand 8, *TGFB1* Transforming growth factor beta 1,*ECM* Extracellular matrix, *FAP* Fibroblast activationprotein, *PDPN* Podoplanin, *MMP2* Matrix metallopeptidase 2,*TME* Tumor microenvironment,*PDGFRB* Platelet-derived growth factor receptor beta, *CCL14* C–C motif chemokine ligand 14, *M2* Type 2 macrophage, *TLS* Tertiary lymphoid structures, *CD74* Cluster of differentiation 74, *HLA-DR* Human leukocyte antigen-DR isotype, *CXCL9* CXC motif chemokine ligand 9, *CCL19* C–C motif chemokine ligand 19

CAFs. Barrier CAFs predominantly localize to tumor margins; closely interact with exhausted $CD8^+$ T cells, $CD4^+$ Tregs, and M2 macrophages, and express markers (COL1A1, ACTA2, and CXCL8) involved in myofibroblast activation, ECM stiffening, and inflammation, forming an immune-excluding barrier associated with poor prognosis [84–88]. Stromal CAFs, characterized by high expression levels of fibroblast activation protein (FAP), podoplanin (PDPN), and matrix metalloproteinase-2 (MMP2) expression, reside deep within the tumor stroma. These CAFs shape the ECM, maintain vascular integrity, and suppress immune infiltration via mechanisms such as IL-6/TGF-β signaling [89]. Myeloid-rich CAFs occupy niches abundant in macrophages and neutrophils near the vasculature, modulating immune suppression through interactions such as GAS6-MERTK, CXCL12-CXC chemokine receptor 4 (CXCR4), and the secretion of extra domain A (EDA) fibronectin (Fn) to polarize macrophages toward the M2 phenotypes [90]. TLS-associated CAFs are found adjacent to tertiary lymphoid structures and express antigen presentation and chemokine genes (CD74, HLA-DR, CXCL9, CCL19, and CCL21) to facilitate adaptive immune responses by recruiting and retaining T/B cells, which is correlated with improved prognosis and enhanced responsiveness to immunotherapy [91].

Crosstalk of CAFs within the TME

CAFs act as central coordinators in the TME through bidirectional communication with malignant cells, immune infiltrates, stromal partners and the extracellular matrix. These dynamic interactions not only fuel tumor cell survival and invasion but also shape local immune responses, modulate hypoxia-driven signaling and drive matrix remodeling. In this section, we describe four major axes of crosstalk in which CAFs participate that collectively determine cancer progression and therapeutic responses (Fig. 2).

Crosstalk between CAFs and tumor cell

CAFs promote malignant progression through reciprocal signaling with cancer cells, activating key oncogenic pathways such as CXCL12-CXCR4, IL-6-STAT3, and integrin-PI3K/AKT-ERK, which collectively sustain tumor cell proliferation, invasion, and therapeutic resistance.

Orchestration of malignant progression and therapeutic resistance

In the TME, CAFs drive tumor progression and therapeutic resistance through multifaceted signaling interactions. With respect to pro-proliferative signals, prostaglandin E2 (PGE2) derived from CAFs directly accelerates tumor proliferation, yet its suppression has paradoxical effects. In neuroblastoma, blocking PGE2 synthesis by targeting microsomal prostaglandin E synthase-1 (mPGES-1) restrains primary tumor growth but paradoxically induces EMT and increases metastasis [92, 93]. Similarly, in glioblastoma, PDGF and TGF-β produced by glioma stem cells (GSCs) regulate CAFs, whereas osteopontin and hepatocyte growth factor (HGF) facilitate GSC enrichment [90]. Additionally, in colorectal cancer (CRC), PDGF-stimulated fibroblasts enhance tumor cell migration and invasion through a stanniocalcin-1 (STC1)-dependent mechanism [94]. CXCL12 derived from CAFs establishes a growth- and survival-promoting niche, driving tumor proliferation via CXCR4 receptor activation and indirectly promoting tumor progression through the recruitment of bone marrow-derived endothelial cells [95]. In pancreatic cancer, CXCL12 secreted by CAFs upregulates SATB-1 in tumor cells, linking CXCL12 signaling to both disease progression and gemcitabine resistance [96]. In intrahepatic cholangiocarcinoma, IL-6 secreted by vascular CAFs (vCAFs) epigenetically upregulates enhancer of zeste homolog 2 (EZH2) to increase malignancy, whereas

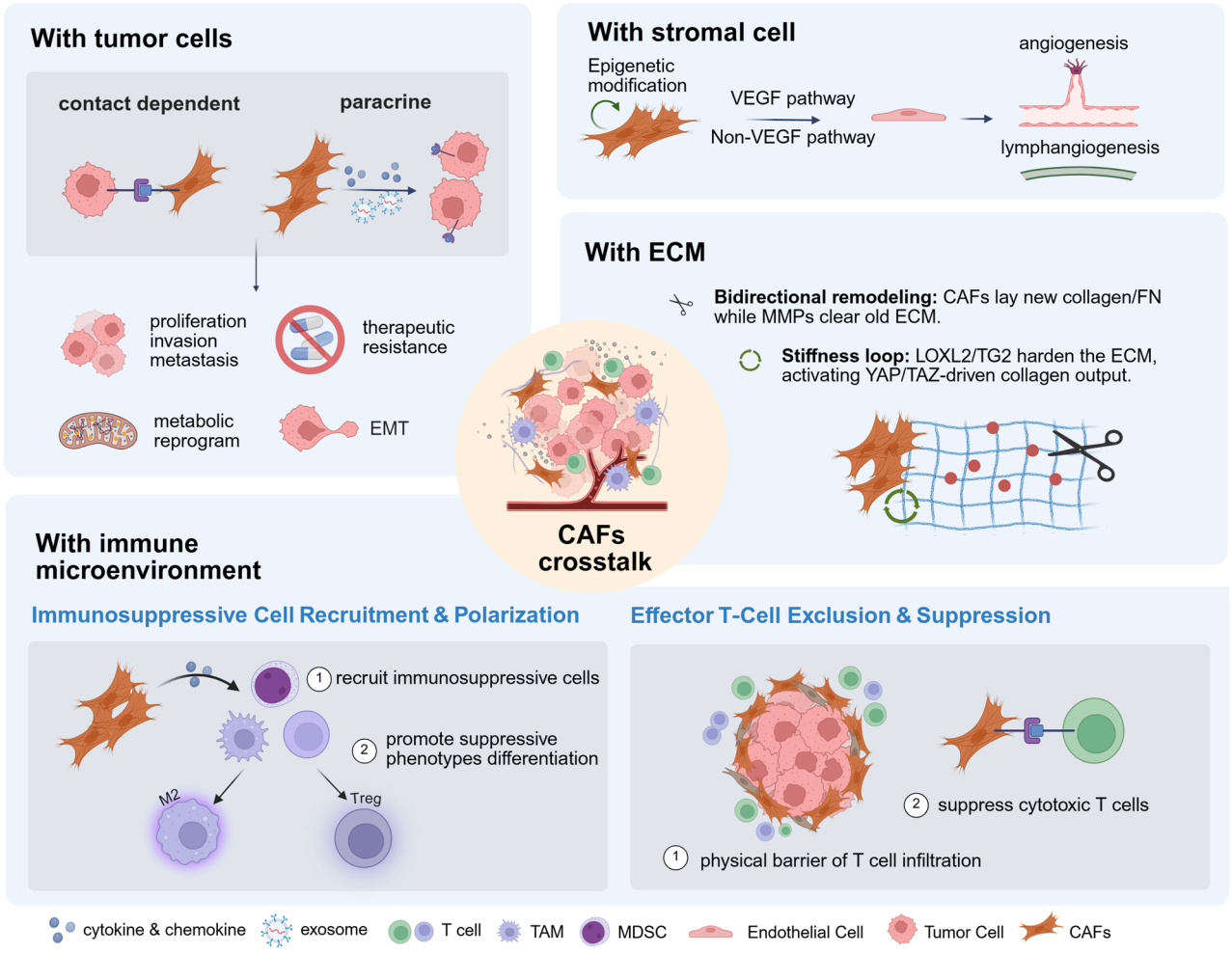

Fig. 2 Crosstalk of CAFs within the tumor microenvironment (TME). CAFs actively communicate with various components within the TME to influence tumor biology. Through direct cell–cell contacts or paracrine signaling, CAFs interact with tumor cells, facilitating proliferation, invasion and metastasis, therapeutic resistance, metabolic reprogramming, and EMT. Additionally, CAFs engage in crosstalk with other stromal cells via VEGF-dependent or non-VEGF pathways to promote angiogenesis and lymphangiogenesis. CAFs also dynamically interact with the ECM, synthesizing new collagen and Fn while degrading old matrix components through MMP. This process is further enhanced by ECM stiffening feedback loops. Besides that, CAFs modulate the immune microenvironment by recruiting and polarizing immunosuppressive cells, thereby suppressing and excluding effector T cell infiltration. CAFs, Cancer-associated fibroblasts; EMT, epithelial-mesenchymal transition; ECM, extracellular matrix; Fn, fibronectin; MMPs, matrix metalloproteinases. Original figure created with BioRender.com

tumor-derived exosomal miR-9-5p reciprocally induces IL-6 overexpression in vCAFs, establishing a bidirectional regulatory loop [97]. In terms of protumorigenic and invasive mechanisms, heterotypic interactions involving the VEGFA-integrin beta-1 (ITGB1) and neuregulin 1 (NRG1)-ERBB3 signaling axes amplify tumor progression across cancer types [98, 99]. FGF2 secreted by CAFs further drives breast cancer cell migration and invasion through FGFR1 activation [100], while heat shock transcription factor 1 (HSF1) activation in CAFs regulates the secretion of TGF-β and stromal cell-derived factor 1 (SDF1) to support malignant transformation [101].

In terms of therapeutic resistance mechanisms, CAFs orchestrate drug tolerance through secretory factors and exosomes. Transitional CXCL14 + myCAFs in lung adenocarcinoma confer resistance to EGFR tyrosine kinase inhibitors (TKIs) [102], whereas IL-6 suppresses p53 activity via the JAK/STAT3 pathway, reducing chemosensitivity in prostate cancer [103]. Exosome-mediated transfer of oncogenic molecules by CAFs represents a critical mechanism of therapeutic resistance. Specifically, exosomes derived from CAFs transport miR-22, which downregulates ERα and PTEN to induce tamoxifen resistance in breast cancer [104], miR-106b which confers gemcitabine resistance in pancreatic cancer [105], and LINC00355 which modulates the miR-34b-5p/ABCB1 axis to promote cisplatin resistance in bladder cancer [106, 107]. Moreover, CAFs reinforce tumor cells and sustain drug resistance by modulating canonical

pathways such as the JAK/STAT3 and integrin–PI3K/AKT–ERK pathways [108, 109].

CAFs promote tumor cell EMT, invasion and stemness acquisition

In the TME, CAFs can drive cancer cell EMT, invasion, and stemness acquisition through multiple, often overlapping mechanisms. This crosstalk is highly reciprocal: tumor cells release cytokines, growth factors, and extracellular vesicles that transform fibroblasts into an active, protumorigenic state, whereas reprogrammed CAFs, in turn, secrete soluble mediators, ECM components, and noncoding RNAs that reinforce malignant phenotypes in tumor cells. This bidirectional communication not only sustains EMT and invasion but also establishes a feed-forward loop that maintains tumor cell stemness and therapeutic resistance within the TME.

Soluble factors secreted by CAFs establish a complex paracrine network that is central to driving EMT, invasion, and stemness [110]. For instance, in anti-PD-1-treated breast cancer, iCAFs reinforce EMT and foster an immunosuppressive niche by activating the TNFα-NF-κB pathway [75]. Specific chemokine axes also play critical roles; for example, CXCL12 derived from CAFs engages CXCR4 and induces IL-1β clustering in gastric cancer cells, markedly enhancing their invasiveness [111], whereas in hepatocellular carcinoma (HCC), CCL5 secreted from CAFs drives EMT via the CCL5–HIF1α–ZEB1 axis [112]. Other mediators derived from CAFs such as MFAP5 and IL-32, activate DLL4/Notch2 and integrin β3–p38 MAPK signaling, respectively, amplifying invasive phenotypes in bladder and breast cancer [113, 114]. Notably, these signals can also promote stemness and therapeutic resistance. In prostate cancer, IL-6 derived from CAFs activates the STAT3/NF-κB cascade to upregulate CXCR7, reinforcing tumor self-renewal [115]. In addition, CAFs contribute to the construction of prometastatic "conduits." FAPα$^+$CD144$^+$ endoCAFs, for example, activate the CD144–β-catenin–STAT3 axis via paracrine signaling to induce the expression of proinvasive factors and the formation of vasculogenic mimicry (VM) networks that provide physical channels for PDAC cell dissemination [76]. Furthermore, Notch2–Jagged1 ligand–receptor interactions strengthen VM network formation and support cellular migration architecture [116].

In addition to soluble factors, CAFs facilitate invasion through direct ECM remodeling and physical interactions with tumor cells. MMPs derived from CAFs are key effectors of ECM degradation. MMP1 activates PAR1 on cancer cells to drive motility, while MMP3 directly cleaves E-cadherin to disrupt intercellular adhesion and promote EMT [117, 118]. Beyond chemical degradation, CAFs can physically guide collective invasion. Heterotypic E-cadherin/N-cadherin adhesions formed between CAFs and tumor cells transmit mechanical forces that recruit β-catenin and reinforce adhesion through α-catenin/vinculin complexes, enabling coordinated migration of cancer cell clusters [119].

A critical and increasingly recognized mode of communication between CAFs and tumors involves the transfer of noncoding RNAs via extracellular vesicles (EVs). CAFs are often enriched in oncogenic miRNAs (e.g., miR-21, miR-210, and miR-155), which are packaged into exosomes that are subsequently internalized by cancer cells, leading to profound reprogramming of tumor behavior [120]. For example, exosomal miR-146a-5p derived from CAFs promotes stemness in urothelial bladder cancer by targeting ARID1A and PRKAA2 [121]. Similarly, exosomal lncRNA H19 functions as a competing endogenous RNA for miR-141, activating the β-catenin pathway and increasing the stemness of CRC cells [122].

Metabolic reprogramming-mediated crosstalk between CAFs and tumor cells

In addition to their roles mentioned above, CAFs also reprogram tumor metabolism to fuel aggressive growth. They remodel how cancer cells use nutrients (glucose, amino acids, and lipids) so that tumor cells have the energy and building blocks they need to proliferate and spread even under stress [123]. CAFs achieve this through different, associated strategies. Exosomes carry metabolic enzymes and regulatory RNAs that increase glycolysis and anabolic pathways and help maintain redox balance under hypoxia or nutrient deprivation once taken up by cancer cells [124]. CAFs overexpress enzymes such as nicotinamide N-methyltransferase (NNMT) in the ovarian cancer stroma, shifting NAD^+ and methyl-donor pools to create a niche that promotes tumor cell migration and growth [125]. CAFs can also establish a lactate shuttle in CRC, resulting in the production of lactate that cancer cells import to drive oxidative phosphorylation and stabilize NF-κB and HIF-1α, thereby enhancing invasion [126]. Beyond lactate exchange, prostate cancer models reveal a more extensive metabolic symbiosis. Tumor cells exploit metabolites derived from CAFs to increase mitochondrial biogenesis and may even acquire functional mitochondria from CAFs through intercellular transfer to maintain redox homeostasis and anabolic capacity under nutrient-limited conditions [127, 128]. By coupling these metabolic changes with their signaling and matrix-remodeling activities, CAFs act as "metabolic copilots," ensuring that tumors remain energetic, adaptable, and invasive.

Crosstalk of CAFs within the immune microenvironment

CAFs orchestrate immune evasion through chemokine networks and physical exclusion barriers, such as

the Endo180⁺ myCAFs niche. CAFs modulate myeloid polarization, T-cell exclusion, and immune-checkpoint engagement via IL-6/STAT3 and Galectin-9–TIM-3 signaling.

Recruitment and polarization of immunosuppressive cells by CAFs

CAFs remodel the tumor immune microenvironment by secreting various chemokines and cytokines, most notably TGF-β, CXCL12, CCL2 and IL-6, which deter effector T-cell activation and chemotaxis while recruiting immunosuppressive myeloid and lymphoid cells [54, 129–134]. For example, in a murine liver tumor model, CAFs engaged the FAP-STAT3-CCL2 axis to increase myeloid-derived suppressor cell accumulation and accelerate tumor growth [135]. In the context of early-stage lung squamous cell carcinoma, PDPN⁺ CAFs upregulate TGF-β1, which is correlated with increased CD204⁺ tumor-associated macrophage (TAM) infiltration [136]. In esophageal squamous cell carcinoma, LRRC15⁺ CAFs partner with SPP1⁺ macrophages to recruit regulatory T cells and establish an immunosuppressive niche [137]. Similarly, in the context of HCC, POSTN⁺ CAFs recruit SPP1⁺ macrophages via IL-6/STAT3 signaling, amplifying local immune suppression [86]. Neutrophils colocalize with IL-6-positive CAFs, resulting in enhanced migratory capacity, longevity, and invasiveness toward pancreatic cancer cells [138].

In addition to recruiting cells, CAFs actively skew the differentiation of infiltrating myeloid and lymphoid cells toward suppressive phenotypes [139]. In gastric cancer, CCL2⁺ CAFs trigger JAK–STAT3 signaling in tumor-infiltrating macrophages, particularly STAT3⁺ TAMs, thereby promoting an immunosuppressive M2 program and tumor progression [140]. Glioblastoma-associated CAFs produce an EDA Fn variant that binds to macrophage TLR4 and drives M2 macrophage polarization [90]. In the context of breast carcinoma, the CAFs-S1 subset secretes CXCL12 to attract CD4⁺ T cells and induce their conversion into $CD25^{High}FOXP3^{High}$ regulatory T cells, weakening effector T-cell function [141]. apCAFs similarly convert naïve CD4⁺ T cells into Tregs, facilitating pancreatic cancer immune escape [47].

Enforcement of T-cell exclusion and immunosuppressive feedback loops mediated by CAFs

CAFs enforce T-cell exclusion and dampen antitumor immunity through multiple, associated mechanisms. First, CAFs can directly eliminate cytotoxic T cells with immune checkpoint ligands. A recent study revealed that CAFs can sample, process and cross-present tumor antigens to CD8⁺ T cells and subsequently trigger their apoptosis through the upregulation of PD-L2 and FASL. Neutralizing either ligand in vitro or in vivo fully restored CD8⁺ T-cell cytotoxicity, proving that CAFs-mediated T-cell killing is antigen dependent and checkpoint driven [142]. Second, myCAFs constitute a physical barrier to T-cell infiltration. For instance, in syngeneic breast cancer models, high densities of myCAFs expressing the Endo180 (Mrc2) receptor generate a dense, αSMA⁺ stroma that excludes CD8⁺ T cells and renders tumors refractory to combined αCTLA-4/αPD-L1 therapy. Genetic deletion of Endo180 selectively depletes these CAFs, reopens the stroma for T-cell entry and restores responsiveness to checkpoint blockade [143]. Finally, CAFs promote T-cell dysfunction via the immune checkpoint pathway. At the tumor margin, ECM-rich CAFs express high levels of Galectin-9, which binds TIM-3 on exhausted CD8⁺ T cells to reinforce their dysfunction and promote immune escape [144]. Consistently, in head and neck squamous cell carcinoma an IFN-induced MHC-Ihi Gal9⁺ CAFs subset "traps" TCF1⁺GZMK⁺ CD8⁺ T cells via the Gal9/TIM-3 axis, driving their dysfunction and maintaining a cold microenvironment [145].

Having outlined how CAFs directly exclude and incapacitate CD8⁺ T cells, it is important to recognize that they do not act alone: CAFs and immunosuppressive myeloid cells engage in reciprocal crosstalk that amplifies and stabilizes the immune barrier. Immunosuppressive TAM subsets (DAB2⁺ and SPP1⁺) increase the activation of FAP⁺ CAFs via TGF-β, PDGF, and ADM signaling, which together stabilize the immune barrier [146]. Additionally, in PDAC, SPP1⁺ TAM-derived CXCL3 activates the expression of CXCR2 in CAFs, inducing a myofibroblastic transition with upregulated αSMA expression and increased type III collagen deposition. This stiffened matrix promotes metastasis and further excludes effector T cells, generating a deleterious positive-feedback loop [147].

Crosstalk of CAFs and stromal cells

CAFs coordinate angiogenesis and lymphangiogenesis through VEGF-dependent and inflammatory cytokine circuits, including IL-8, IL-10, and CCL2, along with PDGF-BB/ERK/JNK and WNT signaling. These processes collectively reshape the vascular niche to support tumor expansion [75, 148, 149].

In a murine breast carcinoma model, stroma-derived CXCL12 recruited endothelial progenitor cells to tumors, providing building blocks for new capillary sprouts. In HCC, hypoxia-induced VEGFA⁺ CAFs establish tight contacts with capillary endothelial cells, significantly accelerating intertumoral angiogenesis and metastatic dissemination [150]. CAFs control is not limited to blood vessels: PDGFRα⁺ITGA11⁺ CAFs bind the SELE receptor on the lymphatic endothelium, triggering SRC-p-VEGFR3-MAPK signaling and lymphatic vessel expansion [151]. Additionally, in cutaneous squamous cell

carcinoma, PAI-1 derived from CAFs drives EndMT of lymphatic endothelial cells through LRP1–AKT/ERK activation, thereby fueling nodal metastasis [152].

Mechanistically, CAFs deploy a broad repertoire of secreted factors, exosomes and direct receptor–ligand contacts [80, 153]. Classical VEGF signaling remains important, as hypoxia-induced HIF-1α/GPER activity increases VEGF-A transcription in CAFs in the context of breast cancer [154]. In CRC, the SULF1$^+$ CAFs subset releases VEGF-A from heparan-sulfate proteoglycans to increase vessel outgrowth [155], while CAFs-derived exosomal circ_0084043 via the circ_0084043/miR-140-3p/HIF-1α axis increases VEGF expression in neighboring endothelial cells [156]. Epigenetic mechanisms also contribute: NNMT-overexpressing oral-squamous-carcinoma CAFs activate an ETS2-VEGFA circuit through NNMT [157]. Additionally, in conjunctival melanoma, fat mass and obesity-associated protein (FTO) in CAFs can effectively eliminate the m6A modifications of VEGFA and EGR1, further increasing VEGF expression [158].

Non-VEGF pathways are equally prominent. A group of proinflammatory cytokine/chemokine circuits predominate this category. PDPN$^+$ CAFs in CRC and metastatic gastric cancer secrete CCL2, which activates endothelial STAT3 and potentiate vascularization [62, 159]. Similarly, chitinase-3-like-1 secreted by CAFs increases the level of IL-8 in an autocrine loop and promotes endothelial tube formation in CRC [160], whereas CD146$^+$ CAFs promote angiogenesis in endothelial cells through the secretion of IL-10 and the activation of JAK1/STAT3 signaling in endometrial carcinoma [161]. In parallel, noninflammatory programs also occur: PDGF-BB secreted by CAFs enhances lymphatic endothelial cell-mediated lymphangiogenesis through PDGFR-β-ERK/JNK signaling [162], while the WNT-centered axis promotes vascularization in both colorectal and breast cancer [163, 164].

Together, these studies show that CAFs fine-tune tumor vascular and lymphatic architecture through intertwined VEGF-dependent and VEGF-independent circuits, which are delivered via paracrine factors, exosomes and juxtacrine signaling, shaping a microenvironment that supports cancer progression and metastasis.

CAFs and extracellular matrix remodeling

CAFs remodel the ECM through collagen and fibronectin deposition, MMP-mediated degradation, and LOXL2/TG2 cross-linking. This remodeling activates YAP/TAZ signaling, establishing a powerful self-reinforcing loop that promotes tumor invasion and therapeutic resistance.

The ECM is a highly dynamic network consisting of a variety of macromolecules such as collagens, glycoproteins and proteoglycans. Its compositional and biomechanical disequilibrium drives cancer progression [165, 166]. Within tumors, CAFs are the principal architects of the extracellular matrix. They produce abundant structural proteins, including collagens and fibronectin, as well as matricellular glycoproteins such as periostin and tenascin-C, and polysaccharides such as hyaluronan. Moreover, CAFs secrete zinc-dependent MMPs that degrade the existing ECM, effectively dismantling and reconstructing the stromal framework [167, 168]. For example, in breast cancer, CAFs require PYCR1-mediated proline biosynthesis to sustain tumor-promoting collagen deposition [169]. In lung adenocarcinoma, MYH11$^+$αSMA$^+$ and FAP$^+$αSMA$^+$ CAFs secrete collagens IV, XI and XII to engineer densely aligned fibers that rigidify the tissue architecture [170].

Crosslinking enzymes such as LOXL2 and TG2 derived from CAFs further increase the stiffness of the ECM [171]. The ensuing mechanical tension activates YAP/TAZ signaling in CAFs [172, 173], which in turn amplifies matrix synthesis and contractility, creating a self-reinforcing "stiff-gets-stiffer" loop. Increased stiffness triggers pro-survival and pro-proliferative pathways in cancer cells [174]; promotes EMT, drug resistance and metastasis; and compresses vessels, leading to hypoxia and more aggressive phenotypes [175, 176]. Moreover, CAFs-mediated remodeling affects pathways related to tumor invasion. Localized MMP activity and actomyosin-driven traction reorient collagen fibers to form tracks that direct tumor cell migration. In bladder cancer, CHI3L1 secreted by PDGFRα$^+$ITGA11$^+$ CAFs reorganizes the peritumoral matrix to facilitate cancer cell invasion [151]. In the context of prostate cancer, CAFs enhance nonmuscle myosin II-mediated cell contractility through PDGFRα, and transfer this mechanical force to Fn via α5β1 integrin, which promotes the directional alignment of Fn fibers, guiding cancer cells to migrate in a specific direction [177]. Collectively, these findings suggest that CAFs orchestrate ECM composition, degradation and cross-linking to modulate tissue mechanics, vascular perfusion, and the cancer cell phenotype.

Therapeutic strategies targeting CAFs

As discussed previously, CAFs are key stromal cells that promote tumor growth, immune evasion, and therapeutic resistance. Multiple strategies are being explored to target CAFs across various tumor types and treatment modalities. Below, we classify CAFs-targeted therapies into three categories (Fig. 3, Table 2): (1) direct targeting of CAFs, (2) inhibition of CAFs-associated signaling pathways, and (3) reprogramming of CAFs.

Direct targeting of CAFs

The first strategy focuses on directly targeting CAFs by identifying markers that are selectively or highly expressed on their surface. These markers include membrane proteins such as FAP, PDGFRβ, and αSMA.

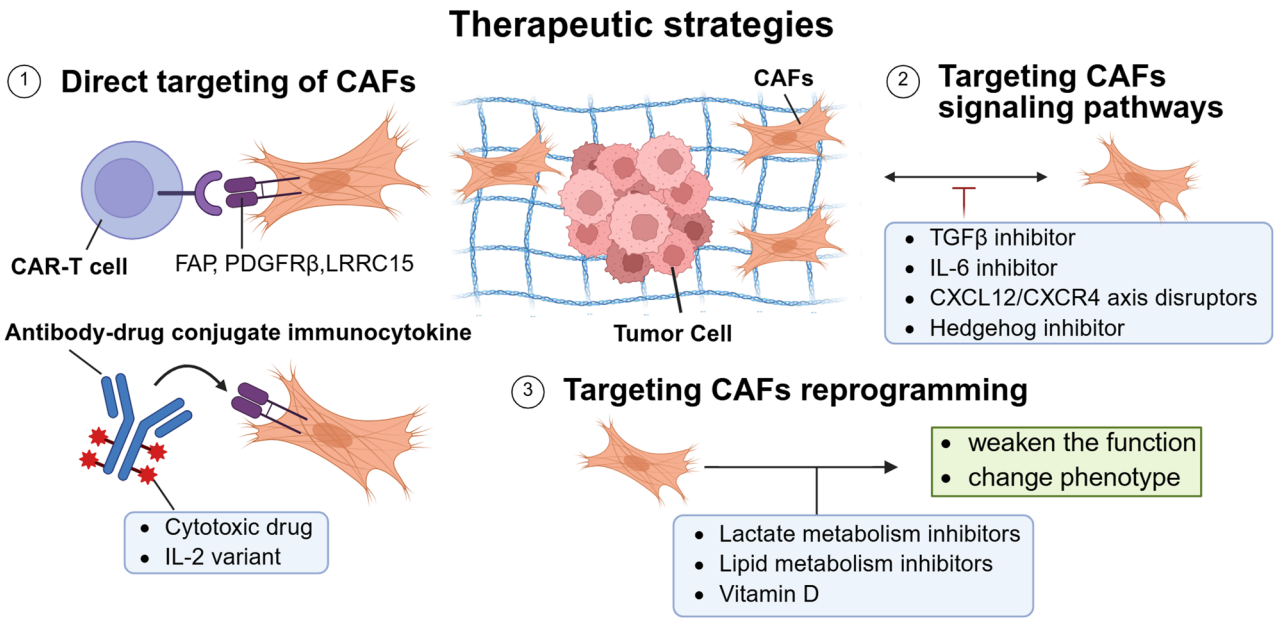

Fig. 3 Therapeutic strategies targeting CAFs. Multiple approaches for targeting CAFs can be employed as therapeutic strategies. Direct targeting of CAFs includes utilizing CAR-T cell therapy, ADCs against commonly expressed CAFs markers such as FAP, PDGFRβ, and LRRC15. Alternatively, functional signaling pathways within CAFs can be targeted, using inhibitors of TGF-β, IL-6, CXCL12/CXCR4 axis disruptors, or Hedgehog signaling inhibitors to block CAFs-mediated tumor-promoting activities. Another promising strategy involves CAFs reprogramming, which aims to either attenuate their pro-tumorigenic functions or convert them into less malignant phenotypes. CAR-T, chimeric antigen receptor T; ADCs, antibody–drug conjugates; FAP, fibroblast activation protein; PDGFRβ, platelet-derived growth factor receptor beta; PDPN, podoplanin; TGF-β, transforming growth factor beta; IL-6, interleukin 6; CXCL12, CXC motif chemokine ligand 12; CXCR4, CXC motif chemokine receptor 4. Original figure created with BioRender.com

Therapeutic approaches include antibodies, antibody–drug conjugates (ADCs), CAR T cells, and vaccines. The goal of these strategies is to eliminate CAFs or deliver cytotoxic agents to the stromal compartment.

FAP

FAP is a serine protease highly expressed on CAFs in more than 90% of epithelial tumors, with limited expression in normal tissues [178]. Consequently, FAP has long been regarded as one of the most representative CAFs targets. First-generation FAP-targeted agents such as sibrotuzumab and talabostat, both of which are humanized monoclonal antibodies, failed to show substantial efficacy in phase II/III clinical trials [179, 180]. One likely reason for this result is that simply binding to or inhibiting FAP$^+$ cells does not induce sufficient cytotoxicity to overcome the tumor-promoting functions of CAFs.

Building on the deeper insights into the heterogeneity of CAFs and FAP biology, next-generation FAP-targeted therapies include CAR-T cells, vaccines, immunocytokines, and radioligands. For example, FAP-CAR-T cells can eliminate FAP$^+$ stromal cells and improve drug delivery. However, their potential toxicity due to FAP$^+$ cell depletion in the bone marrow has been reported [181]. A phase I trial in malignant pleural mesothelioma (NCT01722149) examined the intrapleural infusion of FAP-CAR-T cells and demonstrated good tolerability, with some patients achieving stable disease [182]. These findings suggest that regional delivery can reduce adverse effects. Recently, Wehrli et al. developed dual-function CAR-T cells, that cotarget mesothelin-expressing tumor cells and FAP$^+$ CAFs by secreting a T-cell engager, which demonstrated superior antitumor efficacy in patient-derived and in vivo pancreatic cancer models [183]. FAP-targeted vaccines harness the host immune system to eradicate FAP$^+$ CAFs. In preclinical models, an adenoviral vaccine encoding FAP activated CD8$^+$ T cells, significantly inhibiting both primary tumors and metastases in multidrug-resistant mouse models of colorectal and breast cancer [184]. Various DNA- or epitope-based vaccines have likewise been shown to deplete CAFs, increase drug penetration, and suppress tumor growth [184–187].

FAP has also been used as a "homing target." FAP-IL2v (Simlukafusp alfa, RO6874281), an immunocytokine comprising an anti-FAP antibody fused to a modified IL-2 variant, can localize IL-2 to FAP$^+$ CAFs, thereby activating local T and NK cells [188]. In a first-in-human phase I trial (NCT02627274), Simlukafusp alfa was safe, induced immune activation, and produced objective responses in some patients [189]. A subsequent phase II trial (NCT03386721) in refractory esophageal cancer and recurrent/metastatic cervical squamous cell carcinoma suggested that FAP-IL2v combined with atezolizumab (an anti-PD-L1 antibody) is clinically effective and has

Table 2 Summary of Clinical Trials on CAFs-Targeted Therapeutic Strategies

Therapeutic strategies	Target	Drug name	Study type	Cancer type
Direct targeting of CAFs	FAP	FAP-targeted CAR-T cells	Phase 1 NCT01722149	Malignant Pleural Mesothelioma
		Nectin4/FAP-targeted fourth-generation CAR-T cells	Phase 1 NCT03932565	Advanced malignant solid tumor
		RO6874281(an Immunocytokine Consisting of IL-2v Targeting FAP)	Phase 1 NCT02627274	Advanced and/or metastatic solid tumor
		RO6874281(an Immunocytokine Consisting of IL-2v Targeting FAP)	Phase 2 NCT03386721	Advanced/Metastatic Head and Neck, Oesophageal and Cervical Cancers
	PDGFRα	IMC-3G3(Anti-PDGFRα Monoclonal Antibody)	Phase 1/2 NCT01185964	Advanced Soft Tissue Sarcoma
		Olaratumab (Anti-PDGFRα Monoclonal Antibody)	Phase 3 NCT02451943	Advanced or Metastatic Soft Tissue Sarcoma
	LRRC15	ABBV-085(Antibody–drug conjugate)	Phase 1 NCT02565758	Advanced solid tumors
Inhibiting CAFs-associated signaling pathways	TGF-β	LY2157299	Phase 1/2 NCT01373164	Advanced or Metastatic Unresectable Pancreatic Cancer
		GC1008	Phase 1 NCT00356460	Renal Cell Carcinoma or Malignant Melanoma
		GC1008	Phase 2 NCT01472731	Relapsed malignant glioma
		GC1008	Phase 2 NCT01401062	Metastatic Breast Cancer
		M7824	Phase 1 NCT02517398	Metastatic or Locally Advanced Solid Tumors
	IL-6	Siltuximab	Phase 1/2 NCT00841191	Malignant solid tumors
		Siltuximab	Phase 1/2 NCT04191421	Metastatic Pancreatic Cancer
		Tocilizumab	Phase 2 NCT03999749	Unresectable Stage III or Stage IV Melanoma
	IL-1	Anakinra	Phase 1 NCT02550327	Stage I-III Pancreatic carcinoma
	IL-8	HuMax-IL8	Phase 1 NCT02536469	Advanced Malignant Solid Tumor
	CXCR4	Plerixafor	Phase 1 NCT02179970	Advanced Pancreatic, Ovarian and Colorectal Cancers
		Plerixafor	Phase 2 NCT04177810	Metastatic Pancreatic Cancer
		motixafortide	Phase 2 NCT04543071	Pancreatic Adenocarcinoma
		motixafortide	Phase 2 NCT02826486	Metastatic Pancreatic Cancer
	CXCL12	NOX-A12	Phase 1/2 NCT03168139	Colorectal and Pancreatic Cancer
	Hedgehog	Vismodegib	Phase 2 NCT01088815	Metastatic Adenocarcinoma of the Pancreas

Table 2 (continued)

Therapeutic strategies	Target	Drug name	Study type	Cancer type
CAFs Reprogramming	MCT1	AZD3965	Phase 1 NCT01791595	Advanced Cancer
	Vitamin D Receptor	Paricalcitol	Phase 1 NCT03300921	Resectable Pancreatic Cancer
		Paricalcitol	Phase 2 NCT03331562	Pancreatic Cancer
		Paricalcitol	Phase 2 NCT04524702	Advanced Pancreatic Cancer

Abbreviations: *FAP* Fibroblast activation protein, *IL-2v* Interleukin 2 variant, *IL-6* Interleukin 6, *IL-1* Interleukin 1, *IL-8* Interleukin 8, *PDGFRα* Platelet derived growth factor receptor alpha, *LRRC15* Leucine-rich repeat containing 15,*CXCR4* CXC chemokine receptor type 4, *CXCL12* CXC Motif chemokine ligand 12, *MCT1* Monocarboxylate transporter 1, *TGF-β* Transforming growth factor beta, *VDR* Vitamin D receptor, *CAR-T* Chimeric antigen receptor T cells

manageable safety [190, 191], although further development was ultimately discontinued for strategic reasons rather than a lack of efficacy or safety.

Other FAP-targeting strategies have also shown promise. Near-infrared photoimmunotherapy can selectively remove FAP$^+$ CAFs, restraining tumor growth in an esophageal squamous carcinoma xenograft model without obvious toxicity [192]. FAP-ADCs, such as FAP5-DM1, deliver cytotoxins directly to CAFs, inducing tumor cell apoptosis and disrupting the stromal structure [193]. Similarly, the immunotoxin αFAP-PE38 selectively depletes FAP$^+$ cells and inhibits tumor-promoting factors, whereas in combination with paclitaxel, it enhanced antitumor efficacy in a breast cancer model [194].

Furthermore, FAP-targeted molecular imaging and therapy have shown substantial clinical potential. Compared with conventional 18F-FDG PET/CT imaging, radiotracers such as 68 Ga-FAPI and FAP-2286 can visualize certain tumors with high contrast and detect metastases more sensitively [195, 196]. Therapeutic versions of these radiotracers (e.g., 177Lu-FAPI and 177Lu-FAP-2286) deliver localized radiation to FAP$^+$ stromal cells in advanced solid tumors, resulting in favorable tumor retention, growth suppression, and manageable toxicity in preclinical and early clinical settings [197].

Nevertheless, FAP-directed strategies face important limitations. The heterogeneity of CAFs suggests that not all stromal subsets express FAP at meaningful levels, resulting in incomplete depletion of pathogenic niches and sparing of FAP^{low}-populations. In addition, FAP is not entirely tumor-restricted. Its expression on reparative stromal cells and bone-marrow mesenchymal compartments has been linked to on-target/off-tumor toxicity in preclinical and early clinical studies. Although regional delivery and dose optimization may mitigate these effects, they cannot be entirely prevented. Furthermore, because certain CAFs states can restrain tumor progression, indiscriminate stromal depletion risks paradoxically promoting invasion and immune evasion. These considerations support strategies that selectively target pathogenic FAP$^+$ CAFs subsets or reprogram the phenotype of CAFs and include careful patient selection and safety monitoring.

PDGFRβ and related pathways

PDGFRβ is commonly expressed on CAFs, particularly those involved in desmoplastic reactions and on pericytes [198, 199]. PDGFRβ drives fibroblast proliferation and stromal development. Multiple small-molecule TKIs targeting PDGFR are either in clinical use or under investigation. For instance, multiple studies have indicated that imatinib, a PDGFR/KIT/ABL TKI, can suppress the tumor-promoting functions of CAFs by targeting PDGFRβ. Specifically, imatinib inhibits CAFs-driven proliferation of lung cancer cells [200], blocks CAFs-induced stimulation of lymphatic endothelial cells in cholangiocarcinoma [201], and significantly reduces fibroblast migration [49]. A recent study reported that stromal targeting with blockade of both PDGFRα/β reversed the immunosuppressive microenvironment and enhanced the efficacy of immune checkpoint inhibitors in fibrotic cancer [202]. An additional approach to PDGFRβ$^+$ stromal cells involves the use of bispecific CAR-T cells or T-cell engagers that also target a tumor antigen, thus sparing normal pericytes. Although still in preclinical stages, such strategies highlight the importance of PDGFRβ as a marker for CAFs-targeted therapy. Clinically, PDGFR-directed TKIs are primarily multikinase agents and are associated with class-specific adverse effects, including edema, fatigue, hypertension, and cytopenias. On-target effects on pericytes may destabilize vessels; therefore, the effects of monotherapy are modest, and these agents are preferentially used in combination with other agents or as stromal normalizing partners. Overall, direct PDGFRβ targeting has not yet yielded a breakthrough in clinical trials, reflecting the complex nature of selectively modulating the CAFs-driven stroma.

Leucine-rich repeat containing 15 (LRRC15) is a collagen-binding protein upregulated on activated CAFs particularly those induced by TGF-β, as well as on certain MSCs [203]. LRRC15 + CAFs demonstrate protumor potential, contributing to the immune-excluded and

immune-suppressive TME, and are associated with poor outcomes [204, 205]. The ADC ABBV-085 was developed to target LRRC15 and has demonstrated promising therapeutic efficacy in preclinical studies [206, 207]. In a first-in-human phase I trial (NCT02565758) for advanced solid tumors, ABBV-085 was well tolerated and showed preliminary antitumor activity in patients with osteosarcoma and undifferentiated pleomorphic sarcoma [208, 209]. However, ABBV-085 is associated with a dose-related risk of peripheral neuropathy, which can limit tolerable dosing and treatment schedules. While ABBV-085 has not yet advanced to phase III, it exemplifies a successful CAFs marker-targeted ADC strategy and highlights LRRC15 as a promising CAFs antigen.

Other markers and targets of CAFs

Several additional surface markers on CAFs are being investigated. PDPN is an adhesion molecule expressed by CAFs subsets and mesothelioma cells. Anti-PDPN CAR-T-cell therapy has been evaluated in a Japanese study for mesothelioma, in which PDPN was targeted on tumor cells [210], and PDPN$^+$ CAFs in certain tumors could be targeted via a similar concept. However, PDPN is also expressed on lymphatic vessels and other stromal cells, raising concerns about its specificity. Systemic targeting may pose on-target, off-tumor risks in the lymphatic endothelium, limiting the therapeutic window. Despite its use as a prognostic marker, no major clinical trial has yet targeted PDPN$^+$ CAFs specifically. Endosialin (CD248, TEM1) is a surface glycoprotein on pericytes and some CAFs. The monoclonal antibody *ontuxizumab (MORAb-004)* against endosialin underwent phase I/II testing in solid tumors [211–217]. It was well tolerated but showed minimal efficacy as a monotherapy, with no significant improvement in progression-free survival (PFS). Consequently, its development stalled, underscoring the limited single-agent activity observed to date. CD70 is highly expressed on both tumor cells and CAFs in CRC and PDAC. IL-15-armored CD70-CAR-NK cells effectively eliminated CD70$^+$ tumor cells and CAFs in vitro and significantly reduced tumor burden and prolonged the survival of mouse models, highlighting the promise of targeting both tumor cells and CAFs in desmoplastic solid tumors [218]. These findings suggest that CD70 can be expressed on activated T/B cells and dendritic cells, posing immune on-target risks. Markers such as FSP-1, GPR77, Periostin, Integrin α11, and Thy-1 have been identified on CAFs subsets [86, 199, 219, 220]. While these are not yet targets of approved therapies, they are potential future candidates. For example, GPR77 was detected on a chemoresistant CAFs subset in breast cancer, and blocking C5a signaling reduced the ability of CAFs to support tumors in mice [221]. Periostin, an ECM protein secreted from CAFs, has been shown in in vivo studies to suppress breast cancer cell growth when inhibited [222].

As our understanding of CAFs heterogeneity increases, therapies may be tailored to "bad CAFs" subpopulations defined by distinct markers. Future trials could adopt combinatorial strategies, such as selectively depleting myCAFs by targeting FAP or LRRC15 while simultaneously reprogramming iCAFs through cytokine blockade to comprehensively remodel the TME. At present, FAP remains the most well-validated CAFs surface target, with multiple therapeutic modalities under investigation. PDGFRβ, αSMA, and LRRC15 are key secondary targets, each with agents in clinical development.

Targeting signaling pathways in CAFs

CAFs secrete and respond to various signaling molecules, including TGF-β, interleukins, chemokines, and Hedgehog factors, that drive fibrosis, immunosuppression, and tumor progression. Inhibiting these pathways can help normalize the TME or sensitize tumors to standard therapies. Notably, clinical benefit does not necessarily require the complete elimination of CAFs; instead, blocking key signals can effectively disrupt their protumoral functions. A variety of agents, such as histone deacetylase (HDAC) and smoothened (SMO) inhibitors, have been extensively tested in numerous clinical trials for their ability to modify intracellular signaling and epigenetic regulation in both tumor cells and CAFs precursors [223].

Targeting the TGF-β pathway

TGF-β is a master regulator of the activation of CAFs and immune exclusion. CAFs secrete TGF-β in a paracrine manner to induce tumor cell EMT, and in an autocrine loop that sustains the activity of CAFs through TGF-β receptor signaling [41, 224].

Several TGF-β inhibitors have been developed. Fresolimumab (GC1008), a pan–TGF-β neutralizing antibody, has undergone phase II clinical testing (NCT01401062). In a phase I study (NCT00356460) involving advanced melanoma and renal cell carcinoma, fresolimumab was well tolerated (up to 15 mg/kg), with one patient exhibiting a partial response and several patients with stable disease. A subsequent randomized clinical trial (NCT01401062) in metastatic breast cancer demonstrated that fresolimumab combined with radiotherapy was safe. High doses (10 mg/kg) enhanced systemic immune responses and improved median overall survival [225]. In contrast, a phase II trial in recurrent high-grade glioma (NCT01472731) showed that despite good tumor targeting with (89)Zr-fresolimumab (median SUVmax of 4.6), single-agent treatment offered limited clinical benefit, with a median PFS of only 61 days [226]. These findings suggest that the efficacy of TGF-β blockade

may vary depending on tumor type and is potentially more beneficial when it is combined with radiotherapy or immunotherapy than when it is used as monotherapy. Another TGF-β pathway inhibitor, galunisertib (LY2157299), a small-molecule TGF-β receptor I kinase inhibitor, was evaluated in a randomized phase I/II trial (NCT01373164) for unresectable pancreatic cancer. The combination of galunisertib and gemcitabine modestly increased the median overall survival to 8.9 months compared with 7.1 months, and minimal toxicity was observed [227]. Ongoing studies are examining galunisertib in combination with immunotherapies such as durvalumab. In addition, bintrafusp alfa (M7824), a bifunctional fusion protein composed of the extracellular domain of TGF-β receptor II (TGF-β trap) fused to a human IgG1 antibody targeting PD-L1, has demonstrated TGF-β pathway inhibition and immune activation in early-phase trials (NCT02517398) for advanced solid tumors [228–230]. Taken together, these findings suggest that targeting TGF-β remains a prominent strategy for modulating tumor progression mediated by CAFs.

IL-6/JAK-STAT pathway inhibitors

IL-6 is a proinflammatory cytokine that is frequently produced by CAFs and drives tumor EMT, immune suppression, and cachexia. Targeting IL-6 signaling has shown promise in preclinical models [178, 231]. One key agent is siltuximab, an anti-IL-6 monoclonal antibody that reduces non -small cell lung cancer (NSCLC) tumor xenograft growth by inhibiting CAFs-induced EMT [232]. Siltuximab has completed phase I and II clinical trials (NCT00841191) and is currently under investigation in combination with immunotherapies (NCT04191421). Moreover, tocilizumab, an IL-6 receptor inhibitor, is being evaluated in combination with immunotherapies for unresectable stage III/IV melanoma (NCT03999749). Overall, IL-6 pathway inhibitors remain in early-phase clinical development (phase I/II) for various solid tumors. They exhibit favorable safety profiles and have the potential to suppress CAFs-driven tumor progression.

CXCL12/CXCR4 axis disruptors

In pancreatic and colon tumors, CAFs secrete the chemokine CXCL12, which binds to CXCR4 on both tumor and immune cells, creating an immunosuppressive, pro-survival niche. Disrupting the CXCL12–CXCR4 axis can increase immune infiltration and improve the efficacy of other therapeutic modalities [233].

One such inhibitor is plerixafor (AMD3100), a small-molecule CXCR4 antagonist currently approved for hematopoietic stem cell mobilization. Another agent, BL-8040 (motixafortide), has shown encouraging results in a phase II trial (NCT02826486) for metastatic pancreatic cancer, with a 32% objective response rate and a 77% disease control rate when combined with pembrolizumab and chemotherapy. The median response duration was 7.8 months, and mechanistic analyses revealed increased $CD8^+$ T-cell infiltration and reduced immunosuppressive cell populations [234]. Another example is NOX-A12 (olaptesed pegol), a Spiegelmer aptamer that binds to and neutralizes CXCL12. In a phase I/II study (NCT03168139) for metastatic colorectal and pancreatic cancer, NOX-A12 combined with pembrolizumab induced stable disease or better outcomes in a subset of heavily pretreated patients [235]. These findings suggest that "immune-cold" CAFs-rich tumors may be converted into more "immune-hot" environments by blocking the CXCL12/CXCR4 axis. Overall, these inhibitors remain under early-phase (phase I/II) clinical evaluation across multiple solid tumors, frequently in combination with immunotherapies.

Hedgehog pathway inhibitors

Hedgehog signals from cancer cells can activate stromal fibroblasts, and inhibitors of the Hedgehog pathway have been proposed to collapse the dense CAFs-rich stroma, particularly in PDAC [236]. Some preclinical studies have shown that Hedgehog signaling is uniquely activated in fibroblasts and is differentially increased in myCAFs compared with that in iCAFs. Using smoothened antagonist (LDE225), a Hedgehog pathway inhibitor, impairs tumor growth [66]. Early trials of Hedgehog inhibitors have yielded mixed results. For instance, a first-in-human phase I study of IPI-926, a new chemical entity that suppresses the Hedgehog pathway, in advanced solid tumors demonstrated that it is well tolerated at a dosage of up to 160 mg once daily, with notable single-agent activity in a subset of basal cell carcinoma patients [237]. However, subsequent research on vismodegib, a hedgehog pathway inhibitor, combined with gemcitabine and nab-paclitaxel in patients with metastatic PDAC (NCT01088815) revealed no improvement in efficacy compared with the historical rates observed for chemotherapy alone in patients with newly diagnosed metastatic pancreatic cancer [238]. These findings illustrate that certain "CAFs-depleting" strategies may fail to work as designed, underscoring the need for careful patient selection or their combination with immunotherapies to maximize the benefits of Hedgehog pathway blockade.

Other pathways

Additional CAFs-related signaling molecules (e.g., IL-1β, FGF, IL-8/CXCL8, IL-11, and CCL2) are also under active investigation. IL-1β from fibroinflammatory loops can be targeted by *anakinra* (an IL-1 receptor antagonist) or *canakinumab* (an anti-IL-1β mAb). For instance, a phase Ib trial (NCT02550327) combined anakinra with

chemotherapy in PDAC patients and aimed to reduce inflammation and desmoplasia. Fibroblast growth factors (FGFs) from CAFs can activate FGFRs on tumor cells. Therefore, FGFR inhibitors such as nintedanib or pemigatinib may indirectly modulate crosstalk between CAFs and tumor cells [239, 240]. Nintedanib, a triple kinase inhibitor (FGFR, PDGFR, and VEGFR), was approved for the treatment of lung adenocarcinoma and appears to target the activity of profibrotic CAFs. In NSCLC models, nintedanib reduced CAFs-driven stroma formation, enhanced antitumor immunity, and improved responses to checkpoint blockade [178]. IL-8 (CXCL8) is another chemokine secreted by CAFs that recruits immunosuppressive cells. Anti–IL-8 antibodies (e.g., BMS-986253) are in early trials for solid tumors [241, 242]. Furthermore, IL-11 and CCL2 have been suggested as targets for preclinical intervention [62, 135, 243, 244].

In summary, blocking cytokines, growth factors, and developmental signals secreted by CAFs constitutes a broad therapeutic strategy, with several agents in phase I-II trials. Continued refinement is needed to identify which signaling-targeted approaches yield clinical benefit without undue toxicity.

Targeting the reprogramming of CAFs

CAFs undergo metabolic reprogramming to support tumor growth. For instance, many CAFs rely on glycolysis and produce large amounts of lactate, which cancer cells can take up as fuel [245, 246]. CAFs also engage in fatty acid oxidation (FAO) and nutrient recycling, which supply building blocks to tumor cells. CAFs reprogramming strategies do not aim to directly eliminate CAFs but rather to modify their protumorigenic phenotype or immunosuppressive functions. Here, we focus on three approaches: inhibition of lactate metabolism, suppression of lipid metabolism, and reprogramming of CAFs phenotypes.

Lactate metabolism inhibitors

Lactate, a major metabolic product of CAFs, not only acidifies the TME but also serves as a critical "fuel line" for oxidative tumor cells [247, 248]. Consequently, therapies aimed at inhibiting lactate transporters have shown promise by disrupting this metabolic supply chain and weakening tumor cell metabolism. Additionally, high lactate levels can suppress antitumor immune cells such as T-cells and NK cells; thus, reducing lactate can potentially enhance immune responses [245, 249, 250]. Below, we discuss several lactate metabolism inhibitors that have demonstrated encouraging preclinical or early clinical results. AZD3965 is a first-in-class inhibitor of monocarboxylate transporter 1 (MCT1) that blocks lactate export/import in glycolytic cells. By reducing lactate shuttling, AZD3965 aims to starve tumor cells that depend on stromal lactate and reduce acid-driven immunosuppression. In a phase I trial for advanced solid tumors and diffuse large B-cell lymphoma (NCT01791595), AZD3965 was well tolerated with mostly grade 1–2 adverse events [251, 252]. Other lactate-targeting approaches include direct lactate dehydrogenase (LDH) inhibitors. For example, FX11, an LDH-A inhibitor that is in early development, is being tested preclinically [253]. A recent study revealed that FX11 could reduce tumor growth and improve antitumor immunity in CAFs-rich PDAC tumors [254]. There is also interest in repurposing dichloroacetate (DCA), which inhibits pyruvate dehydrogenase kinase and causes pyruvate accumulation in mitochondria, thereby lowering lactate production. DCA has been administered to certain cancer patients in compassionate-use studies outside of formal clinical trials [255]. Another approach involves buffering or neutralizing the acidic TME, using methods such as oral bicarbonate or proton pump inhibitors, to counteract the effects of lactate. These approaches have resulted in delayed tumor growth in mice, but the clinical evidence is still preliminary.

Lipid metabolism inhibitors

Dysregulation of lipid metabolism is among the most prominent metabolic alterations in cancer [256, 257]. Fatty acids synthase (FASN), a key enzyme in fatty acid synthesis, is significantly upregulated in CAFs, and reprogramming of lipid metabolism in CAFs can increase the migration of CRC cells [258]. With the advancement of research techniques, a distinct lipid-laden CAFs subset that is closely linked to cancer progression was identified [153, 259]. Targeting FAO in CAFs has emerged as an effective strategy for inhibiting peritoneal metastatic CRC growth and metastasis. Studies have shown that CAFs promote colon cancer progression by upregulating CPT1A, a key FAO enzyme. The inhibition of FAO with agents such as etomoxir significantly reduces tumor cell proliferation, invasion, and metastasis [260]. Furthermore, drugs such as perhexiline and trimetazidine, which are used clinically for treating angina, act as CPT1 inhibitors and may be repurposed for use in oncology. Although no FAO inhibitor is currently approved for cancer treatment, preclinical evidence strongly supports FAO as a promising target and encourages the development of new inhibitors or combination therapies.

Reprogramming the phenotype of CAFs

Among the diverse CAFs populations, αSMA$^+$ CAFs, commonly known as myCAFs, are particularly notable for their contractile and fibrotic activities. It is widely believed to be closely associated with angiogenesis and tumor progression within the TME [261]. Recent efforts have focused on reprogramming CAFs phenotypes, with

the goal of transitioning activated fibroblasts to a more quiescent state rather than eliminating them entirely. One prominent example involves vitamin D analogs, such as paricalcitol and calcipotriol, which activate the vitamin D receptor in CAFs. Preclinical research in PDAC has indicated that vitamin D analogs can remodel the dense desmoplastic stroma, improving tissue perfusion and enhancing the efficacy of chemotherapy [262]. The high expression of VDR in stromal fibroblasts in CRC tissue was associated with increased overall survival and PFS. 1,25(OH)2D3 regulates stromal fibroblasts, which exerts protective effects against CRC [263]. On the basis of these findings, several clinical trials (NCT03300921, NCT04524702, and NCT03331562) have been initiated to evaluate the potential effects of paricalcitol on pancreatic tumors [264, 265]. Another avenue for reprogramming αSMA$^+$ CAFs involves indirectly inhibiting TGF-β, given its pivotal role in sustaining myofibroblastic phenotypes. For instance, losartan has shown potential for reducing αSMA-driven fibrosis and improving treatment outcomes in patients with PDAC [266, 267]. Researchers have also investigated antifibrotic compounds such as tranilast and pirfenidone. Pirfenidone, which has been approved for the treatment of pulmonary fibrosis, has been shown to curb CAFs activity and disrupt IL-6/TGF-β signaling in NSCLC models [268]. Although pirfenidone has not yet been used in oncology trials, these results underscore its potential as an adjuvant to limit the function of myofibroblastic CAFs. In addition, modulation of voltage-gated cation channels has recently emerged as another strategy to normalize the activation of CAFs. Activated CAFs display increased potassium, sodium, and calcium conductance, which enhances contractility and ECM remodeling. Pharmacologic inhibition by antiarrhythmic agents partially restores a quiescent, NPF-like phenotype and reduces CAFs-induced EMT and tumor growth in prostate cancer models [269]. Moreover, inhibition of the transient receptor potential ankyrin 1 (TRPA1) channel may also mitigate CAFs-derived protumorigenic signaling, as resveratrol-induced TRPA1 activation in prostate CAFs increases intracellular Ca^{2+} levels and stimulates HGF and VEGF secretion, decreasing tumor cell apoptosis [270]. Together, these findings highlight cation channel modulation as a promising avenue for reprogramming the phenotype of CAFs.

Notably, αSMA$^+$ fibroblasts can help restrain tumor progression by providing structural support in certain contexts. Mouse models of PDAC have shown that completely ablating αSMA$^+$ cells leads to more aggressive, undifferentiated tumors [80]. Consequently, therapies targeting αSMA$^+$ CAFs emphasize modulating or normalizing the phenotype of these cells over total depletion, aiming to mitigate harmful fibrosis and immunosuppression while preserving beneficial stromal functions. Emerging evidence suggests that the Hippo pathway, mainly through YAP1, is critical for maintaining the phenotype of ECM-CAFs by preventing their conversion into more immunogenic Lym-CAFs. This is also a potential route for phenotype switching, expanding strategies for CAFs reprogramming [67]. This broader principle of "CAFs reprogramming", rather than indiscriminate ablation, holds promise for improving therapeutic outcomes in a range of solid tumors.

Conclusion

CAFs have emerged as central orchestrators within the TME and critically influence tumor progression, immune evasion, and therapeutic resistance through diverse and context-dependent mechanisms. The extensive heterogeneity observed in CAFs populations at the phenotypic, functional, and spatial levels underscores both the complexity of their roles and the potential challenges associated with the therapeutic targeting of these cells. Recent advances in multiomics analyses, 3D coculture systems, and spatial transcriptomics have improved our understanding of the biology of CAFs, facilitating the development of more precise and effective therapeutic strategies.

Future research should focus on delineating context-specific roles of CAFs subpopulations, refining therapeutic approaches to avoid adverse stromal depletion, and exploring strategies for reprogramming CAFs to exhibit tumor-suppressive phenotypes. To translate these goals into clinical progress, several knowledge gaps require urgent attention. First, lineage-specific biomarker panels that are analytically validated across tumor types and spatial niches and are translatable in routine clinical settings should be developed. Second, dynamic in vivo imaging should be used to monitor CAFs burden and redistribution during therapy, which serve as pharmacodynamic endpoints. Third, biomarkers of CAFs should be used prospectively to guide patient selection and stratification in clinical trials, employing validated lineage-specific signatures to enrich cohorts and evaluate different CAFs-targeted strategies. Addressing these defined gaps will sharpen translational focus and increase the likelihood that interventions targeting CAFs yield durable clinical benefit across malignancies.

Abbreviations

TME	Tumor microenvironment
CAFs	Cancer-associated fibroblasts
ECM	Extracellular matrix
scRNA-seq	Single-cell RNA sequencing
PDAC	Pancreatic ductal adenocarcinoma
EMT	Epithelial-mesenchymal transition
EndMT	Endothelial-to-mesenchymal transition
Wnt	Wingless/int1
MSCs	Mesenchymal stem cells
MMT	Macrophage-to-myofibroblast transition
TGF-β	Transforming growth factor-β
CTGF	Connective tissue growth factor

COL1A1	Collagen type I alpha 1 chain
OSCC	Oral squamous cell carcinoma
myCAFs	Myofibroblastic CAFs
PDGF	Platelet-derived growth factor
PDGFR	Platelet-derived growth factor receptor
IL-1α/β	Interleukin-1α/β
TNFα	Tumor necrosis factor α
iCAFs	Inflammatory CAFs
NF-κB	Nuclear factor κB
STAT	Signal transducer and activator of transcription
αSMA	α-smooth muscle actin
apCAFs	Antigen-presenting CAFs
MHC	Major histocompatibility complex
FAP	Fibroblast activation protein
PGE2	Prostaglandin E2
mPGES-1	Microsomal prostaglandin E synthase-1
GSCs	Glioma stem cells
HGF	Hepatocyte growth factor
EZH2	Enhancer of zeste homolog 2
TKIs	Tyrosine kinase inhibitors
MMP	Matrix metalloproteinase
endoCAFs	Endothelial-like CAFs
NNMT	Nicotinamide N-methyltransferase
TAM	Tumor-associated macrophage
HCC	Hepatocellular carcinoma
EDA	Extra domain A
CRC	Colorectal cancer
Fn	Fibronectin
ADCs	Antibody-drug conjugates
LRRC15	Leucine-rich repeat containing 15
PDPN	Podoplanin
NSCLC	Non-Small-Cell Lung Cancer
MCT1	Monocarboxylate transporter 1
FAO	Fatty acid oxidation
VEGF	Vascular endothelial growth factor
VEGFA	Vascular endothelial growth factor A
ERK	Extracellular signal-regulated kinase
ERK1/2	Extracellular signal-regulated kinases 1 and 2
PI3K	Phosphoinositide 3-kinase
MAPK	Mitogen-activated protein kinase
JAK	Janus kinase
FGF	Fibroblast growth factor
FGFR1	Fibroblast growth factor receptor 1
CXCL12	CXC motif chemokine ligand 12
CXCR4	CXC motif chemokine receptor 4
GAS6	Growth arrest-specific 6
HIF1α	Hypoxia-inducible factor 1 alpha
YAP1	Yes-associated protein 1
GLUT1	Glucose transporter 1
ACAT2	Actin alpha 2
GDF15	Growth differentiation factor 15
STC1	Stanniocalcin-1
SATB1	Special AT-rich sequence-binding protein 1
vCAFs	Vascular CAFs
ITGB1	Integrin beta-1
NRG1	Neuregulin 1
ERBB3	Erb-B2 receptor tyrosine kinase 3
HSF1	Heat shock transcription factor 1
SDF1	Stromal cell-derived factor 1
PAR1	Protease-activated receptor-1
EVs	Extracellular vesicles
FASL	Fas ligand
CCL2	Chemokine (C-C motif) ligand 2
HDAC	Histone deacetylase
SMO	Smoothened receptor
NOX-A12	Olaptesed pegol
DCA	Dichloroacetate
FASN	Fatty acid synthase
TRPA1	Transient receptor potential ankyrin 1
TLS	Tertiary lymphoid structures
LDH	Lactate dehydrogenase

Authors' contributions
Renbing Jia, Shiqiong Xu and Xiang Gu designed and revised the manuscript. Ziyue Huang, Jie Chen and Tianyu Zhu wrote the manuscript and made the figures. Xiang Gu and Yixiong Zhou polished the manuscript. Jinxin Li and Ho Yin Ng revised and polished the manuscript and the figures. All authors read and approved the final manuscript.

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Data availability
The material supporting the conclusion of this review has been included in the article.

Declarations

Ethics approval and consent to participate
Not applicable.

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