Cell Communication and Signaling

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Cancer-associated fibroblasts: central players in cancer hallmarks and therapeutic resistance

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Abstract
The tumour microenvironment (TME) is now recognized as pivotal to cancer progression and treatment outcomes, alongside cancer cell-intrinsic factors. Among TME constitute, cancer-associated fibroblasts (CAFs) are abundant and actively shape tumour biology. They are heterogenous population arising from multiple origins, and engage in dynamic crosstalk with cancer cells and immune infiltrates to promote virtually all the hallmarks of cancer. By influencing and reinforcement of cancer hallmark traits, CAFs create a pro-tumorigenic niche that also protects cancer cells from therapy, in this way, conferring resistance to conventional therapy. Consequently, CAFs have emerged as central players linking cancer hallmarks to therapeutic resistance. This review discusses the origins and phenotypic diversity of CAFs, the mechanisms of their communication with tumour and immune cells, and how these interactions enforce hallmark capabilities of cancer that underlie treatment resistance. We also highlight preclinical and clinical evidence for CAF-driven drug resistance and examine current strategies to target CAFs or their effects. A deeper understanding of CAF heterogeneity and function could pave the way for novel combination therapies that dismantle the tumour-CAF alliance and improve patient outcomes.

Keywords Cancer-associated fibroblast, Tumour heterogenicity, Tumour microenvironment, Cancer hallmarks, Therapeutic resistance

Introduction

Tumours develop within a complex TME that profoundly influences cancer cell behaviour. Paget's "seed and soil" hypothesis emphasized that the “soil” of the microenvironment is critical for tumour “seeds” to thrive. Among the various stromal components, CAFs are dominant in solid tumours, often constituting the majority of stromal cells. Defined as activated mesenchymal cells, CAFs differ from normal fibroblasts through distinct phenotypes and pro-tumorigenic functions. By secreting growth factors, cytokines, and proteases, and by remodelling the extracellular matrix (ECM), CAFs actively reshape the TME to favour tumour progression.

Crucially, CAFs support the acquisition of hallmark capabilities. While traditionally viewed as cancer cell–intrinsic, these traits are now known to be shaped significantly by stromal interactions. CAFs create a pro-tumour niche that not only nurtures cancer cells but also shields them from external stresses, including therapy [1]. Therapeutic resistance, a major barrier in cancer treatment, is influenced not only by cancer cell mutations but also by the CAF-rich TME. CAFs activate survival pathways in tumour cells, build physical and immunosuppressive barriers, and secrete dense ECM components that impede

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drug delivery [2, 3]. These features compromise the efficacy of conventional therapy.

CAFs are not a homogenous population. Single-cell and lineage-tracing studies reveal substantial heterogeneity in origin, markers, and function. While many CAF subsets promote tumour growth, others may play context-dependent or even restraining roles [4, 5]. Nevertheless, high CAF activity generally correlates with poor prognosis and therapy resistance. This review examines CAF origins, heterogeneity, and mechanisms of interaction with cancer and immune cells. We also explore emerging strategies to target CAFs or their functions while accounting for their diversity. Integrating CAF-focused interventions may be essential for overcoming resistance and improving cancer treatment outcomes.

The versatility of CAFs in cancer development and treatment

CAFs origin and heterogeneity

CAFs originate from a variety of sources, reflecting their inherent heterogeneity. Most commonly, they derive from local resident fibroblasts that become "activated" in the cancer context, a process co-opted from normal wound-healing programs [6]. Upon injury or inflammation, quiescent fibroblasts differentiate into proliferative, contractile myofibroblasts (marked by α-SMA and FAP), which tumours exploit to drive continuous stromal remodelling. Beyond fibroblasts, other precursors including bone marrow-derived MSCs, pericytes, endothelial and epithelial cells (via EMT/EndMT), adipocytes, stellate, mesothelial, and smooth muscle cells can also convert into CAFs, establishing a diverse cellular origin (Fig. 1).

The diversification of CAFs is driven by persistent tumour-derived stimuli in the TME. Paracrine factors such as TGF-β, FGFs, PDGF, and IL-1 activate stromal fibroblasts [7–9]. In addition, the tumour releases metabolites by-products and exosomes that can epigenetically reprogram stromal cells [10]. For instance, methylmalonic acid and exosomal miR-146a from cancer cells can induce CAF-like phenotypes [11]. Moreover, increased ECM stiffness in tumours enhances CAF formation via mechanotransduction (e.g., integrin/FAK signalling) [12, 13]. Once established, CAFs exhibit substantial heterogeneity in markers, transcriptomes, and function. Not all CAFs promote tumour progression—some subsets may even restrain it. This has spurred interest in CAF subclassification. For example, CD200 + CAFs in EGFR-mutant lung cancer were associated with longer progression-free survival, while CD10 + GPR77 + CAFs promote cancer

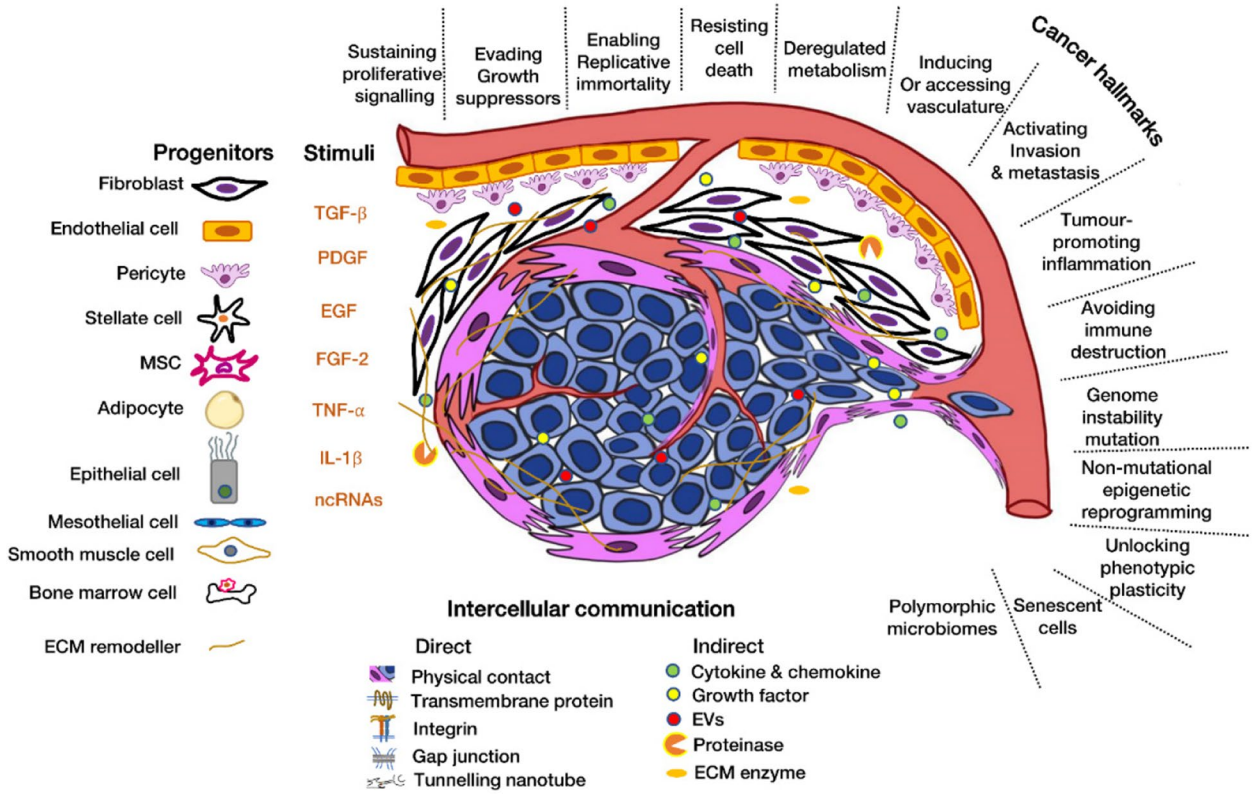

Fig. 1 Overview of the origins, intercellular interactions and functions of CAFs. This schematic illustrates the diverse cellular progenitors that can give rise to CAFs under various stimuli. Once activated, CAFs engage in direct and indirect communication with tumour and stromal cells, thereby influencing the formation and reinforcement of cancer hallmark traits

stemness and chemoresistance [14, 15]. These examples underscore how CAF heterogeneity leads to divergent functions, dissecting CAF subsets is crucial to designing therapies that selectively disrupt tumour-promoting CAFs while preserving or reprogramming neutral or beneficial ones.

Beyond cellular origins, CAFs diversify into functional subclasses that occupy distinct spatial niches and deploy different secretomes. These subtype-resolved programs differentially reinforce cancer hallmarks—ECM desmoplasia and solid stress (limiting drug penetration), inflammation-driven stemness and survival, antigen-presentation–like immune modulation, metabolic buffering of oxidative stress, angiogenic remodelling, and therapy-induced senescence that seeds relapse. A comparative view clarifies which CAFs to suppress, reprogram, or preserve, enabling selective interventions rather than bulk depletion (Table 1).

Table 1 Functional heterogeneity of CAFs across tumour ecosystems

Subtype	Enrichment/markers	Dominant programs	Hallmark impact	Drug resistance	Potential intervention
myCAF	α-SMA, FAP, LOX-high	ECM deposition, solid stress, FAK/YAP	Desmoplasia, invasion	Low perfusion, drug delivery barrier	Hyaluronan/collagen modulation, LOX/FAK inhibitors
iCAF	IL-6/IL-8/CXCL12	JAK/STAT3, immune exclusion	Proliferation, stemness	Chemo/TKI tolerance, ICI resistance	IL-6/JAK inhibitors; CXCR4 blockade
apCAF	MHC-II, CD74	Antigen-presentation-like	T-cell dysfunction	ICI resistance	Reprogramming (ATRA/VDR), TGF-β tuning
meCAF	MCT4 +, metabolic enzymes	Reverse-Warburg, metabolite shuttling	Metabolic flexibility	ROS/energy stress tolerance	Metabolic co-targeting (OXPHOS/glutamine)
Lipid-CAF	VEGF-A +, lipid droplets	Angiogenesis	Vascular remodelling	Abnormal perfusion	Anti-angiogenic + stroma normalization
Senescent CAF	SASP (IL-6/IL-1/TNF), p16/SA-β-gal	Persistent inflammation	Recurrence post-therapy	Post-chemo relapse	Senolytics/senomorphics

Communication with tumour and immune cells in the TME

Tumours do not progress in isolation, instead, there is constant reciprocal crosstalk between cancer cells and CAFs in the TME. CAFs typically localize in close proximity to malignant cells and profoundly influence tumour cell fate through both direct cell–cell contacts and a rich secretory communication network. Through these interactions, CAFs bolster fundamental cancer hallmarks in the tumour cells, all of which contribute to therapeutic resistance.

Direct cell–cell interaction

CAFs engage in direct physical interactions with cancer cells that enable exchange of signals, organelles, and metabolites through several mechanisms: (i) ligands-transmembrane receptors interactions. CAF-expressed surface proteins can bind complementary receptors on cancer cells, altering adhesion and enhancing tumour cell motility and invasiveness [16]. (ii) Cell adhesion molecules, such as integrins on either cell type facilitate binding. For example, integrin α5β1 mediates firm adhesion between CAFs and gastric carcinoma cells, promoting peritoneal dissemination [17]. (iii) Juxtacrine signalling. Physical cell–cell contact can activate signalling pathways in tumour cells. For instance, co-culture of CAFs with non-small cell lung cancer (NSCLC) cells was shown to activate Hedgehog signalling in the cancer cells, illustrating how direct contact can induce oncogenic pathways in tumour cells [18]. (iv) Gap junctions. CAFs and cancer cells can form gap junction channels (e.g. via connexin 43) that allow direct transfer of ions, metabolites, and small molecules. Through unidirectional gap junctional coupling, CAFs have been reported to shuttle metabolites of aerobic glycolysis into ovarian cells, thereby fuelling tumour growth [19]. (v) Tunnelling nanotubes (TNTs) or tumour microtubes. CAFs can form long, actin-based membrane tunnelling nanotubes connecting to cancer cells, serving as conduits for exchange of organelles and vesicles [20]. A recent study found that CAFs in leukaemia can transfer intact mitochondria to acute lymphoblastic leukaemia cells via TNTs, rescuing the cancer cells from chemotherapy-induced oxidative stress [21].

Paracrine signalling and secreted factors

CAFs are prolific secretors of soluble factors and vesicles that diffuse through the TME and influence tumour and immune cells at both short and long range. The CAF secretome includes growth factors (e.g., FGFs, HGF, TGF-β1, PDGF, etc.), chemokines and cytokines (e.g., CXCL12/SDF-1, IL-6, IL-8), pro-angiogenic factors (VEGF, angiopoietins), proteases (MMPs, cathepsins), ECM components and remodelling enzymes (e.g., collagens, fibronectin, LOX), and EVs carrying nucleic acids and proteins [22, 23]. Many of these signals mirror those produced by tumour cells themselves, creating a reinforcing positive feedback loop between the cancer cells and stroma. For example, CAF-derived TGF-β1 and CXCL12 can synergistically enhance tumour invasiveness and at the same time recruit endothelial progenitor cells to form new blood vessels, which feed the growing tumour mass. These same factors also feedback to further recruit or activate CAFs at the tumour's invasive front, establishing a self-perpetuating cycle that drives continuous invasion and metastasis [24]. Moreover, EVs, especially exosomes, from CAFs further facilitate intercellular communication by shuttling regulatory RNAs. In breast cancer, CAFs-secreted exosomal lncRNA LINC01614 enhanced glutamine uptake in lung adenocarcinoma [25]. Through this rich repertoire of direct contacts and paracrine signals, CAFs profoundly reprogram the behaviour of tumour cells and other stromal constituents.

How CAFs enforce hallmark traits and drive therapeutic resistance

CAFs orchestrate malignant phenotypes across nearly all cancer hallmarks (Fig. 2) through two tightly coupled communication modes: (i) direct cell–cell contacts (integrin/FAK, juxtacrine Notch/HH, gap junctions and TNT-mediated organelle transfer), and (ii) paracrine secretomes (IL-6/IL-8, CXCL12, HGF/FGF/TGF-β, exosomal ncRNAs). These communication axes converge on tumour-intrinsic programs—sustained proliferation (RAS-MAPK), EMT and invasion, metabolic rewiring (reverse-Warburg, mitochondrial donation), immune exclusion (CXCL12-CXCR4, TGF-β), and stress tolerance (ROS buffering/anti-apoptosis)—thereby establishing bypass circuits that blunt the intended effects of cytotoxics, targeted agents, and immunotherapy. In this section, we map CAF-driven support for each hallmark to concrete resistance phenotypes and highlight representative intervention points.

Sustained proliferation and survival signalling

Promoting proliferation

CAFs secrete a plethora of growth factors that activate proliferative signalling pathways (e.g., RAS/MAPK, PI3K/

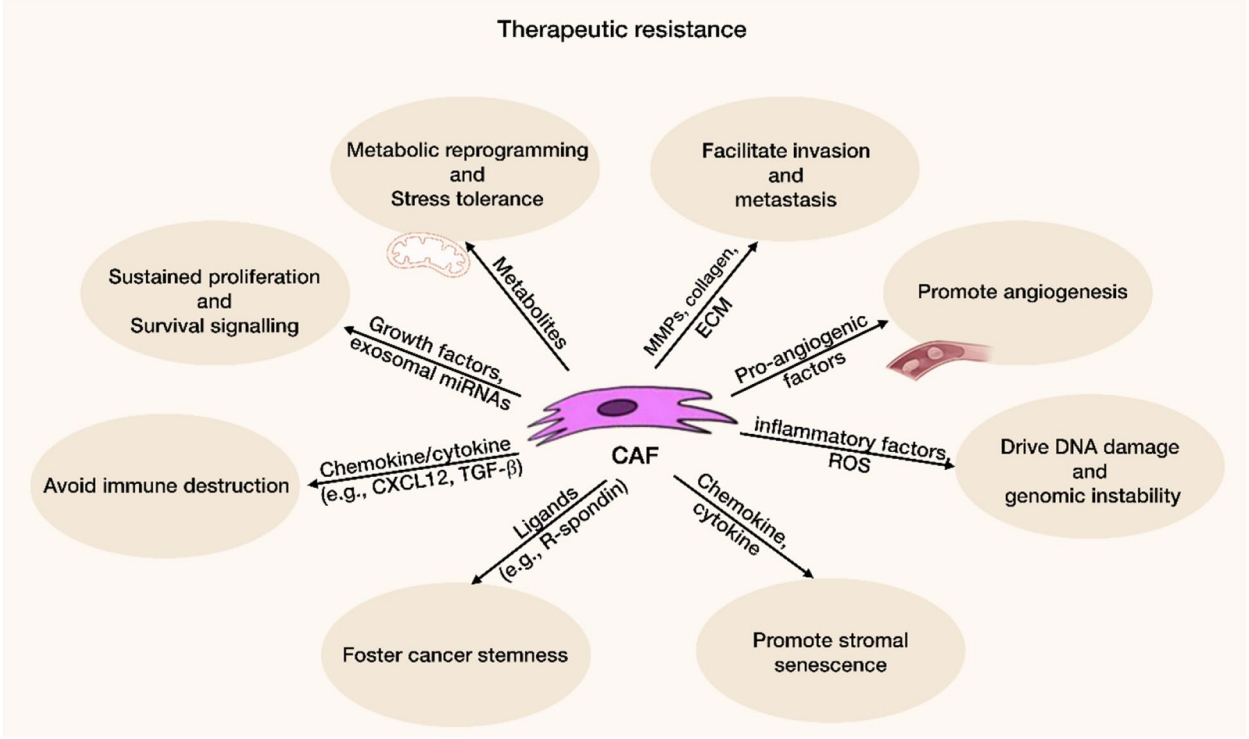

Fig. 2 CAF as a central player in driving therapeutic resistance through fostering hallmark traits. CAFs can enforce hallmark traits to either limit the drug penetration or mediate the properties of TME, thus driving therapeutic resistance of cancer

AKT, etc.) in cancer cells. For example, IL-8 from CAFs can upregulate NRP1 in gallbladder cancer cells, driving DNA synthesis and cell division [26]. These paracrine signals make cancer cells less reliant on their own oncogenic driver mutations for proliferation. Consequently, even if a targeted therapy inhibits an oncogenic kinase (e.g., EGFR or BRAF), alternative growth inputs from CAFs may sustain tumour cell division. This has been observed in EGFR-mutant lung cancer where HGF from stromal fibroblasts can reactivate ERK signalling despite EGFR inhibition, causing drug resistance, which is analogous to providing a "bypass" track for growth signals [27]. In addition, CAFs can release exosomal ncRNAs that activate growth pathways. For instance, CAF exosomes delivering miR-3656 to oesophageal cancer cells stimulated the PI3K/AKT pathway to promote proliferation [28]. By supplying these myriad growth stimuli, CAFs help tumour cells to continue proliferating even under therapies aimed at growth arrest.

Enhancing survival and anti-apoptotic pathways

CAFs also provide signals that enable cancer cells to resist cell death through upregulating pro-survival pathways in tumour cells, increasing expression of anti-apoptotic proteins and activating survival kinases. For example, miR-522 secreted by CAFs suppressed ferroptosis through targeting ALOX15 and promoted acquired chemoresistance in gastric cancer [29]. The net effect is that cancer cells in a CAF-rich stroma are more resilient: even when chemotherapy induces DNA damage or targeted therapy blocks a key survival signal, cancer cells still receive parallel rescue signals from CAFs that enable them to evade apoptosis. It was observed striking accumulation of CAFs in PDAC patients with poor response or resistance to gemcitabine, the deoxycytidine accumulated in the conditioned media of CAFs could reduce gemcitabine toxicity [30]. In addition, CAFs-secreted IL-6 could activate STAT3 signalling that raised Bcl2 and cyclin D1 to blunt gemcitabine-induced cell death in cholangiocarcinoma [31]. These evidence from both co-culture experiments or in vivo studies further support that the presence of CAFs frequently protects cancer cells from drug-induced cell death, confirming the tangible impact of CAF-mediated survival support, making this CAF-driven resistance to apoptosis as a major barrier to effective therapy-induced tumour cell killing.

Metabolic reprogramming and stress tolerance

Cancer cells frequently rewire their metabolism, a hallmark enabling rapid growth and survival in harsh environments. CAFs substantially aid this metabolic reprogramming and help tumour cells tolerate metabolic stress or therapy-induced stress.

Metabolic symbiosis between CAFs and cancer cells

CAFs undergo metabolic alterations that complement the metabolic needs of cancer cells. Notably, CAFs often adopt the "reverse Warburg effect," whereby they themselves perform aerobic glycolysis and produce energy-rich metabolites (lactate, pyruvate, ketone bodies) which are exported and taken up by cancer cells to fuel oxidative phosphorylation [32]. By increasing their glycolytic flux and even engaging autophagy, CAFs supply tumour cells with alternative nutrients. For example, CAF-derived lactate is taken up by prostate carcinoma cells and utilized in the TCA cycle, promoting more efficient energy production [33]. In pancreatic cancer, pancreatic stellate cell (CAF)–secreted alanine has been shown to support tumour cell tricarboxylic acid cycle metabolism when glucose is scarce, thereby sustaining tumour growth [34]. CAFs can also augment a tumour's addiction to glutamine by secreting glutamine or other amino acids, which cancer cells readily consume [8]. Through these cooperative exchanges, CAFs buffer tumour cells against nutrient deprivation – a condition often exacerbated by poor perfusion in solid tumours or by therapies aiming to "starve" the cancer.

Enhancing oxidative stress tolerance

The metabolic coupling extends to handling metabolic waste and oxidative stress. CAFs display an important mediator for "metabolic coupling" or "energy transferring" between cancer cells and stromal TME. Under glucose limitation, CAFs can reuse lactate produced by glycolysis-enhanced cancer cells via monoc-carboxylate transporter 1 (MCT1) as a metabolic fuel, which may locally modulate lactate accumulation and acidosis while sustaining fibrotic and immunosuppressive programs [35]. Conversely, hypoxia-induced, MCT4-expressing CAFs can export lactate, protecting neighbouring cancer cells from acidotoxicity and death [36]. Thus, CAFs operate a bidirectional "lactate shuttle" through MCT isoforms (MCT1/MCT4) that dynamically regulate metabolite flow within the TME. In addition, CAFs release metabolites to "feed" cancer cells to combat oxidative damage. For example, cysteine supplied by CAFs could enhance ferroptosis resistance by glutathione synthesis in pancreatic ductal adenocarcinoma (PDAC) [37]. CAFs released glutathione precursor could inhibit the production of reactive oxygen species (ROS) in prostate cancer cells, thus antagonizing drug-induced cell death [38]. Interestingly, direct transfer of mitochondria from CAFs to cancer cells has been observed, which can boost the respiratory capacity and stress resistance of tumour cells under chemotherapy-induced oxidative stress [21]. Chronic inflammation driven by CAFs can also select for cancer cells with higher stress tolerance and can induce DNA damage in tumour cells that leads to adaptive

metabolic changes. CAF-driven inflammatory cytokines (e.g., CXCL1, IL-6) provoke ROS bursts and rewire the tumour DNA damage repair, which not only enhances radio/chemo-tolerance but also couples to metabolic adaptation (e.g., glycolytic shift or boosted antioxidant programs) [39, 40]. Altogether, by rewiring local metabolism and managing stressors, CAFs enable cancer cells to survive conditions (nutrient starvation, hypoxia, high ROS) that might otherwise be lethal or sensitize them to therapy. This metabolic support diminishes the efficacy of treatments that target cancer metabolism or rely on creating metabolic/oxidative stress in the tumour.

Invasion, metastasis, and therapeutic escape

Metastasis, the leading cause of cancer mortality, relies heavily on stromal support, with CAFs acting as pivotal enablers [41]. CAFs facilitate local invasion by secreting matrix-degrading enzymes (e.g., MMP-2, MMP-9, cathepsins) [42], and remodelling the ECM through LOX-mediated collagen crosslinking and contraction, forming aligned fibres and radial tracks that guide cancer cell migration [43]. They also secrete factors like TGF-β, HGF, and EGF ligands to induce epithelial–mesenchymal transition (EMT), enhancing cell motility and drug resistance. For instance, THBS2 + CAFs in colorectal cancer drive oxaliplatin resistance via EMT induction. Moreover, recent studies show CAFs promote vasculogenic mimicry in pancreatic cancer, supporting metastasis via endothelial-like reprogramming of tumour cells [44, 45].

At metastatic sites, disseminated tumour cells recruit or reprogram local fibroblasts into CAFs, establishing a pro-metastatic niche that promotes angiogenesis and immune evasion [46]. CAF-rich tumours, especially those with a dense, desmoplastic stroma, are linked to increased aggressiveness and reduced therapy response. Recent studies show that senescent myCAFs in PDAC orchestrate immunosuppression and dense ECM, underpinning aggressive biology and weak immunotherapy responses [47]. By enabling invasion, EMT, and metastatic niche formation, CAFs not only drive tumour spread but also facilitate escape from localized treatments, contributing to relapse and therapeutic failure.

Angiogenesis and desmoplastic barrier

Angiogenesis, the formation of new blood vessels, is essential for tumours to grow beyond a certain size by ensuring adequate oxygen and nutrient supply. CAFs are potent promoters of angiogenesis in the TME. They secrete pro-angiogenic factors such as VEGF-A, FGF-2, PDGF-C, and angiopoietin-1, and also recruit and activate endothelial cells and pericytes to form neovasculature. The neovessels stimulated by CAFs help sustain tumour expansion and also provide additional routes for metastasis (via the circulation). It was indicated that oncogenic KRAS could transform the phenotype of CAFs into lipid-laden CAFs, which produce VEGF-A to spur angiogenesis in CRC [48]. This poses greater challenges to the existing treatment strategies, as CAFs can undermine these therapies by supplying alternate angiogenic signals. Paradoxically, while promoting blood vessel formation, CAFs also contribute to a desmoplastic barrier that impedes drug delivery [49]. The same CAFs that secrete angiogenic factors also produce copious amounts of ECM (collagens, hyaluronan, fibronectin) which accumulate in the tumour stroma. This fibrotic stromal reaction increases the solid stress within the tumour and compresses blood vessels, often rendering them aberrant and poorly perfused. The result is an irregular, high-pressure vascular network where blood flow is heterogeneous and delivery of drugs (especially large molecules) is inefficient. This "physical resistance" mechanism means that even if cancer cells are intrinsically sensitive to a drug, the drug may never reach them at therapeutic concentrations due to the stromal barrier erected largely by CAF activity [50]. Furthermore, areas of the tumour that are poorly perfused tend to be hypoxic, and hypoxic cancer cells are often more resistant to radiation and certain chemotherapies [51].

In short, CAF-driven angiogenesis feeds the tumour but in an uncoordinated manner, while CAF-driven desmoplasia creates a barrier to treatment. Both aspects, abnormal vasculature and high stromal pressure, contribute to reduced efficacy of systemic therapies like chemotherapy and to the sanctuary of subsets of cancer cells in hypoxic, protected niches.

Immune evasion and immunotherapy resistance

Avoiding destruction by the immune system is a core hallmark of cancer, and CAFs are prime enablers of tumour immune evasion, contributing to resistance against immunotherapies [52]. One key mechanism is immune cell exclusion: CAFs create physical and chemical barriers—such as dense ECM and chemokines like CXCL12—that trap cytotoxic T cells (CTLs) at the tumour periphery, preventing infiltration [53]. Inhibiting TGF-β has been shown to reverse this exclusion, particularly in FAP + CAF-rich tumours [54]. Additionally, the dense ECM laid by CAFs can act as a literal physical barrier to immune cell movement, and CAFs can upregulate molecules like periostin that alter immune cell localization [55].

Beyond exclusion, CAFs also secrete immunosuppressive factors that blunt the activity of immune cells. Molecules such as TNF-stimulated factor 6 (TSG-6) was observed in immune checkpoint therapy-resistance pancreatic tumours and majorly expressed by CAFs, where enhanced macrophages expressing immunosuppressive phenotypes. CAFs-secreted fibronectin with the extra

domain A variant can recruit and polarize immune cells toward pro-tumour phenotypes [56]. Another emerging mechanism is immune checkpoint expression: certain CAF subsets can express PD-L1 or PD-L2, as well as FASL, which can directly suppress or kill effector T cells [57]. CAFs can also induce neighbouring immune cells to upregulate other checkpoints. The cumulative effect of these CAF-mediated actions is a profoundly immunosuppressive tumour milieu, where cancer cells are shielded from immune attack. Consequently, tumours with high CAF content often respond poorly to immunotherapies like PD-1/PD-L1 checkpoint inhibitors, simply because there are insufficient CTLs reaching the tumour or those that do are rendered dysfunctional [58]. Clinically, CAF-rich "immune desert" tumours in cancers like melanoma and pancreatic cancer often fail to respond to checkpoint inhibitors [59], prompting interest in combination therapies targeting CAFs or their signals alongside immunotherapy.

Cancer stemness and phenotypic plasticity

Tumours often harbour a subpopulation of cells with stem cell–like properties (cancer stem cells, CSCs) that can self-renew and drive relapse. CAFs have been shown to foster cancer cell stemness and maintain phenotypic plasticity within tumours, thereby contributing to therapeutic resistance. They secrete cytokines like IL-6, IL-8, and CXCL12 that activate pathways such as STAT3, NF-κB, and Wnt/β-catenin—key regulators of stemness. For example, IL-6 from CAFs induces STAT3-mediated upregulation of stemness genes (e.g., Nanog, Sox2) [60], while IL-8 enhances stem-like traits in ovarian cancer cells [61]. Some CAFs also produce Wnt ligands and R-spondin, reinforcing undifferentiated cancer states via Wnt/β-catenin signalling [62, 63]. CAF-secreted exosomes may further contribute to the CSC niche [64].

Direct cell–cell contact also promotes stemness. β1-integrin interactions can activate Notch signalling, maintaining progenitor-like properties in cancer cells. A particularly aggressive CAF subset—$CD10^{+}GPR77^{+}$—secretes high IL-6 and IL-8 levels, enriching tumours with CSCs and conferring chemoresistance. In preclinical models, blocking GPR77 reduced CSCs and restored treatment sensitivity [65], underscoring the causal role of CAFs in maintaining cancer stemness. Interestingly, a recent study showed that a CAF-senescence score positively correlates with immunosuppressive immune-cell infiltration, and that senescent CAFs promote CSC traits and metastasis via a SOX4–CTHRC1–Notch1 axis, underscoring that CAF diversity is linked to the formation of cancer stemness [66]. These findings demonstrated that CAFs undermine therapy efficacy and allow tumour regrowth by nurturing drug-resistant CSCs and enabling phenotypic switching. Targeting CAF-induced stemness pathways is thus a promising strategy to improve long-term cancer control and prevent relapse.

Genomic instability and DNA repair

Genomic instability, an increased rate of mutations, is a driving force in cancer evolution and can lead to the emergence of therapy-resistant clones. While genetic alterations originate within cancer cells, CAFs can indirectly influence this hallmark by creating conditions that foster DNA damage or by altering DNA repair processes in tumour cells.

Chronic inflammation in the TME, to which CAFs are major contributors, can be genotoxic. CAFs secrete inflammatory mediators (e.g. IL-1β, IL-6, TNFα) and induce accumulation of ROS and nitric oxide in the milieu. Elevated ROS can damage DNA in nearby cancer cells, causing mutations or chromosomal instability. Over time, this can increase tumour heterogeneity and spawn subclones that withstand therapies (for example, a subclone with a TP53 mutation or a drug-resistant oncogenic variant might be selected) [67]. Additionally, CAFs can target DNA repair pathways in cancer cells. There is evidence that CAFs induced lncRNA DNM3OS expression in oesophageal cancer to confer radioresistance via regulating DNA damage response [68].

Furthermore, therapy itself can induce DNA damage not only in cancer cells but also in stromal cells. DNA-damaged CAFs might become senescent and adopt senescence-associated secretory phenotype (SASP), which could impair proper DNA damage response in cancer cells through constant NF-κB activation, etc. [69]. While this area is still being unravelled, the concept is that CAF-rich tumours might have an accelerated evolutionary trajectory, where each round of therapy and interaction with stromal factors results in selection of more genetically divergent and resistant populations. This contributes to the difficulty of achieving long-term control, as new mutations and tumour variants keep arising under the protective wing of the CAFs.

Stromal senescence and therapy-induced remodelling

Cellular senescence in the stroma—particularly within CAFs—has direct consequences for cancer treatment outcomes. Clinical and experimental evidence shows that senescent CAFs emerge after therapy and correlate with poorer responses. In NSCLC, radiotherapy-induced, senescence-like CAFs fostered radioresistance in neighbouring tumour cells [70]. A recent study indicated that docetaxel/cisplatin robustly induced CAF senescence accompanied by malignant reinforcement through metabolic rewiring and SASP activation [71]. In oesophageal cancer, hypoxia-induced senescent fibroblasts heightened tumour stemness and blunted chemotherapy efficacy [72]. Importantly, senescence also compromises

immunotherapy: in mouse models and therapy-induced senescence contexts, the accumulation of senescent cells reduced intratumour CD8⁺ T-cell infiltration/activation and limited ICI efficacy, whereas senolytic clearance with ABT263 (Navitoclax) restored immune homeostasis—reversing myeloid-cell immunosuppression on single-cell analysis—and rescued response to ICI [73]. Mechanistically, therapy-induced senescent CAFs acquire a SASP—rich in IL-6/IL-8, growth factors, and MMPs—that paracrinally reprograms tumour cells toward survival, immune evasion, and treatment resistance, overlapping with canonical CAF secretions. Notably, senescent myCAFs suppress NK-cell cytotoxicity, whereas their depletion restores NK-mediated tumour control [74].

Thus, partial tumour killing coupled with stromal senescence can reshape the TME into a more relapse-permissive niche—a therapeutic paradox wherein cytotoxic benefit is offset by stromal reprogramming. For example, (i) senolytics such as navitoclax given before or together with ICI can clear therapy-induced senescent cells, restore CD8⁺ T-cell responses, and rescue immunotherapy efficacy [73]; (ii) disrupting the CAF-derived CXCL12–CXCR4 axis alleviates T-cell exclusion and synergizes with anti-PD-L1 in desmoplastic tumours [75]; and (iii) VDR agonist–mediated stromal reprogramming ("stroma normalization") enhances drug delivery and potentiates chemotherapy in pancreas-like fibrotic settings [76]. Together, these examples illustrate that co-targeting tumour and stromal/CAF programs can outperform tumour-centric monotherapies and offers a tractable path to reduce relapse and extend survival.

CAFs and cancer hallmarks of polymorphic microbiomes

Beyond the above-mentioned cancer hallmarks, polymorphic microbiomes are one of the fourth newly added dimensions for understanding cancer hallmarks [77]. The microbes, including the resident bacteria, fungi, and viruses that vary among individuals, play a pivotal role in human diseases, such as diabetes, obesity, non-alcoholic fatty liver disease, and even cancer, etc. There is growing evidence showing that human microbiomes can evolve throughout life following exposure to intrinsic factors (e.g., age, hormones, and stress) and extrinsic environments (e.g., food, drugs, and lifestyle). In the last several decades, studies conducting high-throughput techniques to decipher the distinct landscape of microbiota have demonstrated that this ecosystem contributes to cancer susceptibility, progression and response to chemotherapeutic drugs, and provide metabolite, immunity and resistant properties to the cellular component of TME [78]. It has been extensively documented the intricate host-microbiome interactions and the potency of particular microbiota being biomarkers for personalized medicine against cancer [79]. Although microbe–CAF axis remains underexplored, emerging reports now link specific microbes and their metabolites to CAF programs. Recent work in colorectal cancer shows that pathobionts (e.g., *Fusobacterium nucleatum*) can engage CAFs, amplifying pro-inflammatory cytokines, ROS generation and metabolic rewiring—thereby potentiating colorectal cancer progression [80]. In parallel, microbial metabolites (e.g., secondary bile acids, butyrate, and LPS etc.) can reprogram CAF metabolism and secretory profiles, suggesting a bidirectional microbe–CAF crosstalk that shapes tumour ecology [81–84]. In addition, a high-fat diet (HFD) was shown to reshape gut microbiota within the intestinal stem-cell niche, which in turn favoured colonic MSCs acquiring CAF-like properties (e.g., Wnt-biased signalling), driving crypt hyperproliferation and priming colon cancer initiation [85]. Collectively, these observations indicate that microbiome composition and activity can both influences, and be influenced by, CAF-like stromal states, opening testable avenues for diet/microbiome–stroma co-intervention.

Targeting CAFs: therapeutic implications

Given the multifaceted role of CAFs in driving tumour progression and resistance, there is a strong rationale for therapeutically targeting CAFs or their products as a complement to direct cancer cell–targeted therapies. Indeed, it has become clear that attacking only the cancer cells while ignoring the stroma is unlikely to yield durable responses, since CAFs will continue to support and protect any remaining malignant cells. A number of strategies have been pursued to disrupt the tumour–CAF alliance (Fig. 3, Table 2).

Eliminating CAFs

One straightforward strategy is to eliminate CAFs from the TME, in hopes of removing the supportive "soil" for the cancer "seed." This approach targets markers thought to be relatively specific to CAFs. A prominent example is FAP, a cell surface serine protease highly expressed by many CAFs and to a lesser extent by some normal stromal cells during wound healing. Preclinical studies showed that genetic ablation of FAP + fibroblasts in mice can unleash immune attack on tumours: in a lung cancer model, deleting FAP + cells led to accumulation of CD8 + T cells and tumour necrosis [120]. Similarly, vaccine-based strategies against FAP have been tested. A DNA vaccine that induces immune responses to FAP significantly reduced FAP + CAF numbers and was associated with increased intratumoral chemo uptake and enhanced T cell activity, overcoming immune tolerance in mouse models of colon and breast cancer [121]. Other approaches include CAR T-cells engineered to target FAP on CAFs, which in preclinical studies resulted in suppressed tumour growth and boosted immunity though

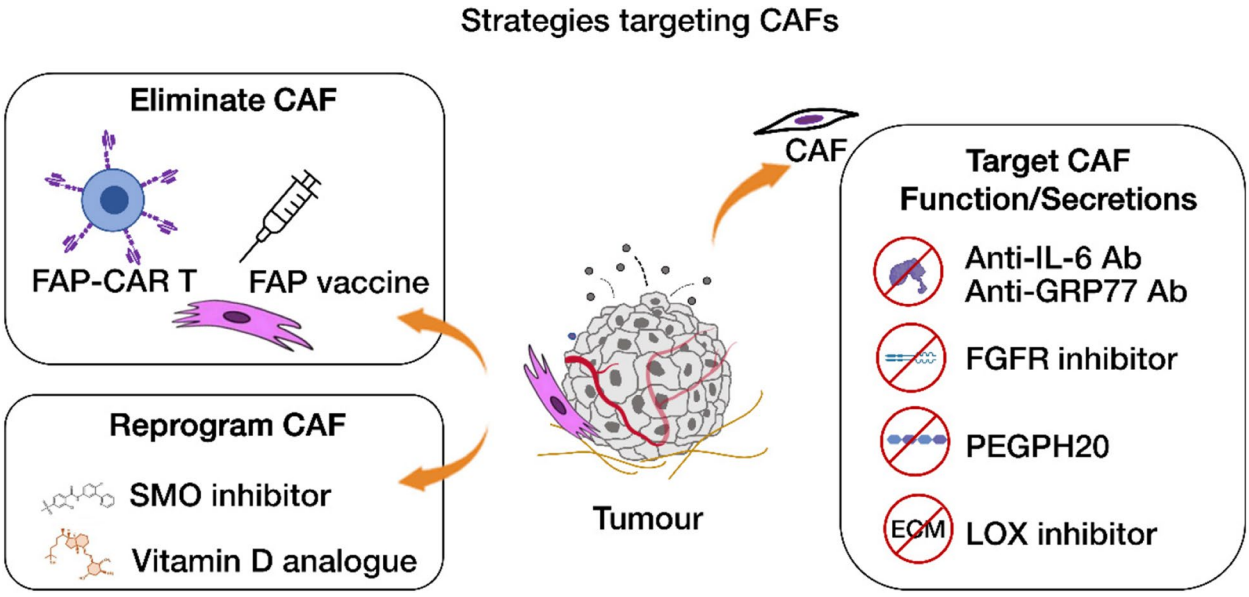

Fig. 3 Strategies targeting CAFs. Current strategies of targeting CAFs include elimination of CAFs by CAR-T cells or vaccination, reprogram CAFs by vitamin D analogues or corresponding inhibitors targeting specific signalling pathways, and rescue the function or secretions of CAFs by blocking key factors

with cautionary notes on potential toxicity [91]. These approaches demonstrate that depleting CAFs can indeed make tumours more vulnerable, especially by relieving immune suppression and improving drug delivery.

However, a challenge with CAF depletion is specificity and safety. FAP, for instance, is not exclusively on CAFs; it is also found on some normal cells (e.g., in bone marrow, skeletal muscle fibroblasts) and has functional roles. Complete elimination of FAP + cells in mouse models caused side effects like cachexia and anaemia [122]. Similarly, targeting α-SMA + myofibroblasts in PDAC (using a genetic approach) unexpectedly led to more aggressive tumours and reduced survival [123]. These findings illustrate that simply wiping out all CAFs can sometimes backfire, perhaps by removing the subset of CAFs that keep the most aggressive cancer cells in check or by damaging normal tissue repair processes. Therefore, if CAF depletion is attempted, it likely needs to be partial or selective for the most deleterious CAF subpopulations. Identifying unique markers for "bad" CAFs versus "good" CAFs is an area of ongoing research.

Rewiring CAFs to a quiescent or anti-tumour state

Rather than eliminating CAFs, an alternative approach is to reprogram them into a quiescent or even tumour-suppressive state, capitalizing on their mesenchymal plasticity. One promising strategy involves activating nuclear hormone receptors. For example, pancreatic stellate cells expressing the vitamin D receptor (VDR) can be driven into a lipid-storing, quiescent state by calcipotriol (a vitamin D analogue). In PDAC models, VDR activation "renormalized" the stroma, reduced CAF activity and cytokine secretion, and enhanced gemcitabine delivery and efficacy [124]. This concept is being tested in a phase II trial combining a vitamin D analogue with immunotherapy in PDAC [125].

Another strategy targets key signalling pathways maintaining CAF activation. Blocking TGF-β, a major fibroblast activator, can reduce CAF activity, though systemic effects on immune and tumour cells must be considered. Notably, TGF-β inhibition can shift inflammatory iCAFs toward the less protumour myCAF subtype, lowering IL-6 and other tumour-promoting signals [126]. Similarly, inhibition of developmental pathways like Hedgehog signalling—exploited by breast cancer cells to induce CAF activation—has been shown to restore chemotherapy sensitivity in preclinical models using SMO inhibitors [127]. Although clinical trials in PDAC have yielded mixed results, they support the concept of stromal "normalization" through pathway inhibition. Other reprogramming tactics include enhancing CAFs' immunoregulatory potential. For instance, antigen-presenting CAFs (apCAFs) may be redirected to support T cell responses, while modifying CAF-derived chemokines could attract immune effectors rather than suppressors.

Overall, reprogramming strategies aim to shift CAFs from tumour enablers to neutral or even beneficial players. These approaches reduce tumour-promoting signals while avoiding the risks associated with total CAF depletion. Clinical trials using vitamin D analogues and ATRA in PDAC and liver cancer are actively exploring this therapeutic avenue.

Table 2 Current therapeutic strategies targeting CAFs

Strategy	Pharmacological target	Drug	Cancer	Mechanism/Action	Ref/Clinical Trial
Reduce CAF abundance	FAPα	DNA vaccine	Breast cancer	Reduce FAPα + CAF population; combine with antitumour vaccine	[86, 87]
		CAR T-cells	Multiple cancers	Reduce FAPα CAF population; combine with immunotherapy	[88, 89] Phase I: NCT03932565
		Oncolytic adenovirus	CRC	Reduce FAPα CAF population	[90, 91]
		Talabostat (BXCL701)	PC	Reduce FAPα CAF population	[92] Phase I: NCT04123574
		HA@DSP-pep-DS	PC	A transformable nanoparticle loaded with Doxorubicin can "dock" with CAFs to facilitate penetration of doxorubicin	[93]
		F19	CRC	A monoclonal antibody targeting FAPα	NCT00004042
		Sibrotuzumab (BIBH 1)	Lung cancer, CRC	An inhibitor directly against FAP	Phase I: NCT02209727 Phase II: NCT02198274
		RO6874813	Advanced or metastatic cancer	A bispecific antibody and fusion protein (anti-FAP& anti-death receptor 5)	Phase I: NCT02558140
		RO6874281	Melanoma, RCC, breast cancer, HNSCC	A bispecific antibody and fusion protein (anti-FAP& IL2); combined with Pembrolizumab/Atezolizumab/Bevacizumab	Phase I: NCT03875079, NCT03063762
		FAPI	Multiple cancers	An FAP inhibitor that was developed for PET imaging and radioligand therapy	[94]
		Nano-PIT	Breast cancer	A nanoparticle-based photoimmunotherapy that eliminate FAP + CAFs and suppress CXCL12 secretion and ECM deposition	[95]
Reduce CAF abundance	α-SMA	Cellax™-DTX	PDAC	A carboxymethylcellulose-docetaxel nanoparticle that concentrates in SMA + CAFs and leads to long-term degradation	[96]
	CAF population	nab-paclitaxel	PDAC	Eliminate CAF population; Combination with Gemcitabine	[97–99]
	miR-142-3p	MSI-N1014	CRC	Reduce the transformation of NFs into CAFs in part by reducing TGF-β1 and IL-6 expression of CRC cells; Increase 5-FU efficacy	[100]
	Hyaluronic acid	PEGPH20	PDAC, NCSLC	Reduce stromal components and improve the delivery of immune- and chemotherapy	Phase I: NCT02563548 Phase II: NCT03634332
	Tenascin C	Navitoclax-loaded nanoliposomes modified with peptide FH (FH-SSL-Nav)	HCC	Eradicate CAF population via a tenascin C-targeted nanoliposome with navitoclax	[101]
	HDAC	Entinostat	NSCLC, melanoma, CRC	Prevent CAFs generation and activation by inhibiting HDAC; combine with Pembrolizumab/Nivolumab/Azacitidine	Phase II: NCT02437136, NCT01928576
		Vorinostat	NSCLC	Prevent CAFs generation and activation by inhibiting HDAC; combine with Pembrolizumab	Phase I/II: NCT02638090
		Mocetinostat	NSCLC	Pembrolizumab; combined with durvalumab	Phase I/II: NCT02805660

Table 2 (continued)

Strategy	Pharmacological target	Drug	Cancer	Mechanism/Action	Ref/Clinical Trial
Inhibit CAF function	TGF-β	Fresolimumab (GC1008)	Multiple cancers	A monoclonal antibody that can neutralize all isoforms of human TGF-β	Phase I/II: NCT02581787
		Galunisertib (LY2157299)	Ovarian cancer, CRC	A TGF-β receptor 1 inhibitor that suppresses fibrosis; Combination treatment with chemotherapy	[102] Phase I/II: NCT03470350
		Tranilast	Multiple cancers	Reduce CAF secretory factors and the infiltration of immune suppressor cell types; Enhance dendritic cell-based vaccines	[103]
		Bintrafusp alfa (M7824)	Multiple cancers	A bifunctional fusion protein targeting TGF-β and PD-L1	Phase II: NCT04396886
	CXCL12-CXCR4 axis	Olaptesed (NOX-A12)	PDAC	A CXCL12 inhibitor that reduces iCAFs secreted CXCL12 and CD8 T cell infiltration	NCT03168139
		Motixafortide (BL-8040)	PDAC	A CXCR4 antagonist that reduces iCAFs secreted CXCL12 and CD8 T cell infiltration	NCT02826486
		Plerixafor (AMD3100)	Endometrial cancer, PC, HNSCC	A CXCR4 antagonist that leads to T cell accumulation; Combined with chemotherapy	[75, 104] Phase II: NCT04058145
	IL-6	Retinoid acid (RA)	PDAC	Reduce IL-6 secretion of CAFs	[105]
		Metformin (MCT4)	Ovarian cancer, metastatic prostate cancer	Inhibit NF-κB signalling in CAFs to downregulate IL-6; Enhance antitumour effects of cisplatin	[106] Phase II: NCT04926155
		Siltuximab (CNTO 328)	PC	An anti- IL-6 mAb	Phase I/II: NCT04191421
Inhibit CAF function	IL-6	Tocilizumab (MCLA-128)	Breast cancer	An anti-IL-6 receptor antibody that suppresses activated CAF; combined with Pertuzumab/Transtuzumab	Phase I: NCT03135171
	Sonic hedgehog pathway	Cyclopamine (CPA)	PDAC	Inhibit CAF activation and stromal deposition; Combination treatment with paclitaxel	[107]
		Vismodegib (GDC-0449)	PC, PDAC, breast cancer, orbital and periocular basal cell carcinoma	Inhibit the activity of CAFs and collagen; Increase delivery of chemotherapy	[108] Phase IV: NCT02436408
		IPI-926	PC	Inhibit the activity of CAFs and collagen fibers; Combined with gemcitabine	Phase I/II: NCT01130142
	LOX	PXS-5505A	Myeodysplastic syndrome, liver cancer, PC, melanoma, glioblastoma, head and neck cancer	Inhibit all LOX family to reduce fibrosis	[109] Phase II: NCT04676529
		Simtuzumab	PDAC	Inhibit ECM enzyme, LOX-like 2	Simtuzumab
	IL-1β	Canakinumab	NSCLC	An IL-1β inhibitor	Phase III: NCT03447769
	the Na+/K+ATPase	Cardiac glycosides	-	Prevent CAF differentiation	[110]

Table 2 (continued)

Strategy	Pharmacological target	Drug	Cancer	Mechanism/Action	Ref/Clinical Trial
Inhibit CAF function	Caveolin-1	Chloroquine	Ductal carcinoma	Inhibit autophagic/lysosomal degradation to restore caveolin-1 in CAFs and prevent CAF conversion	[111]/ NCT01023477
	CAF-related genes	Cetuximab	HNSCC	Upregulate CAF markers and cytokines (e.g., CXCL12) that correlate to EMT	[112]
	Caspase-3 activation	Bortezomib + Panobinostat	Breast cancer, oesophageal cancer, stomach cancer	Inhibit CAFs viability; Increase the effect 5-FU and docetaxel	[113]
	NOTCH signalling	RO4929097	skin squamous cell, PC	Suppress expansion of CAFs	[114] Phase II: NCT01232829
	FAK activity	Defactinib (VS-6063)	NSLC	Inhibit CAFs migration/invasion and decrease ECM deposition by CAFs by suppressing FAK activity	Phase II: NCT01951690
		GSK2256098	PC	Reduce CAF secretome by inhibiting FAK activity	Phase II: NCT02428270
	Tyrosine kinase	Erdafitinib	NSCLC, urothelial cancer, oesophageal cancer	A Pan-EGFR tyrosine kinase inhibitor that prevents CAFs activation and secretome production	NCT02699606
Reprogram CAF status	Retinol store in CAF	ATRA	PDAC	Induce quiescence of CAF progenitor cells; Combination treatment with gemcitabine and paclitaxel	[115, 116] Phase I: NCT03307148 Phase II: NCT04241276 (Not yet recruiting)
	Vitamin D receptor	Calcipotriol	PDAC	Revert activated CAFs to quiescence via binding to vitamin D receptor; Increase intra-tumoral gemcitabine intake	[76]
		Paricalcitol	PDAC	Induce a quiescent phenotype for CAFs highly expressed vitamin D receptor	Phase II: NCT03331562
		1α,25-dihydroxyvitamin D_3 [1,25$(OH)_2D_3$]	CRC	Inhibit the activation of CAFs	[117]
		Vitamin D3	PDAC	Induce a quiescent phenotype for CAFs highly expressed vitamin D receptor	NCT03472833
	The synthesis and utilization of lipid in CAFs	Gold nanoparticles (GNPs)	PC	Transform CAFs to quiescence	[118]
	P53	Nutlin-3a	PDAC	Reprogram activated PSCs to quiescence via triggering p53 activation	[119]
	IL-1R	Anakinra	PDAC	Switch iCAF to a myCAF phenotype	NCT02550327

Abbreviation: *CRC* Colorectal cancer, *PC* Pancreatic cancer, *PDAC* Pancreatic ductal adenocarcinoma, *HCC* Hepatocellular carcinoma, *HNSCC* Head and neck squamous cell carcinoma, *NSCLC* Non-small cell lung cancer, *CRC* Colorectal cancer, *RCC* Renal cell carcinoma, *ATRA* all-trans retinoic acid

Targeting the CAF function/secretions

Cytokine/chemokine inhibitors

CAFs' production of IL-6 has made the IL-6/STAT3 pathway a major target. Tocilizumab, an anti-IL-6 receptor antibody, and siltuximab, an anti-IL-6 antibody, are drugs already used in inflammatory diseases and tested in cancer [128, 129]. JAK inhibitors (downstream of IL-6) like ruxolitinib have also been tried in combination with chemo for cancers with high IL-6 [130]. Similarly, CCL2 (MCP-1) released by CAFs (and tumour cells) recruits macrophages; MCP-1 (anti-CCL2) showed some transient blockade of monocyte infiltration in trials, though tumours eventually found alternative pathways [131]. These. approaches aim to dismantle the CAF-driven inflammatory loop that protects the tumour.

Growth factor signalling blockade

CAF-derived HGF can cause resistance to EGFR and BRAF inhibitors, so MET inhibitors or HGF antibodies can be used alongside those targeted therapies. For

example, stromal HGF activated MET and produced immediate, innate resistance to RAF inhibition in BRAF-mutant melanoma and neutralizing HGF/MET restored sensitivity [132]. CAF-derived FGF promotes angiogenesis and resistance to VEGF inhibitors, so FGFR inhibitors might complement anti-VEGF therapy. For instance, FGF2 levels rise under VEGF-axis blockade and FGFR inhibition reduces tumour growth in anti-VEGF-resistant models; similarly, angiokinase inhibitors with FGFR activity (e.g., nintedanib) can overcome bevacizumab resistance in preclinical colorectal cancer models [133, 134]. In short, for several major CAF-secreted growth factors (HGF, FGF), there are existing agents (MET/anti-HGF, FGFR inhibitors) that can be rationally paired with tumour-directed targeted therapies to neutralize stromal bypass signalling and delay resistance.

Protease and ECM targeting

CAF-secreted proteases and crosslinking enzymes—most prominently MMPs and LOX—reshape collagen/fibronectin architectures, stiffen the stroma, and facilitate invasion and metastatic spread. Historically, broad-spectrum MMP inhibitors suffered from dose-limiting toxicity and lack of benefit; however, more selective agents or targeting MMP activators/upstream cues are being revisited in biomarker-enriched settings, underscoring the need for context- and subtype-specific deployment [135]. LOX inhibition (e.g., BAPN) reduces collagen crosslinking, decompresses vessels, and has shown less metastasis and improved intratumoural drug perfusion in preclinical models, supporting LOX as a matrix-normalization lever [135].

Another ECM component, hyaluronan, often produced by CAFs, can elevate interstitial fluid pressure and compress vasculature, particularly in desmoplastic tumours such as PDAC [136]. PEGPH20, a PEGylated hyaluronidase enzyme, was used in trials to degrade hyaluronan in PDAC, yielding improved perfusion and some efficacy gains when combined with chemo, though with some thrombotic side effects (NCT03634332). While PEGPH20 is not a CAF-depleting drug, it targets a major CAF product to collapse the stromal barrier and enhance drug delivery—a concept that aligns with "stroma normalization" rather than pan-CAF ablation.

In addition, CAF-driven mechanotransduction a complementary level. CAF-expressed integrins α5β1 and αVβ3 bind fibronectin/collagen and activate FAK–SRC–YAP signalling in both CAFs and adjacent tumour cells, aligning ECM fibres into invasion "tracks," maintaining high interstitial fluid pressure, and sustaining drug tolerance [137, 138]. Therapeutically, α5β1/αVβ3 on CAFs are druggable with anti-integrin antibodies/RGD-mimetics and FAK inhibitors, which disrupt CAF–ECM adhesion and downstream mechanotransduction. In line with the reviewer's point on integrins as targets, this argues for combination strategies that pair ECM normalization (e.g., HA or LOX modulation) with integrin/FAK pathway inhibition to collapse stromal barriers, reduce IFP, dismantle contact-guided migration, and re-sensitize tumours to systemic therapy.

Inhibiting CAF-specific signals

Targeting CAF-specific markers is a promising strategy. GPR77, expressed on chemoresistance-promoting CAFs, was neutralized by an antibody in preclinical studies, restoring chemosensitivity [139]. CD10 is another marker that could be targeted with future specific approaches. Combining stroma-targeted therapies with conventional treatments often yields synergistic effects. Examples include CXCR4 inhibitors with anti-PD-L1 immunotherapy to reverse immune exclusion [52]; dual TGF-β and PD-L1 blockade to restore T-cell infiltration, and hyaluronidase combined with chemotherapy to enhance drug delivery in PDAC [54]. However, clinical translation requires caution: excessive stromal disruption, such as complete CAF ablation or Hedgehog inhibition, has at times accelerated tumour growth in animal models. This highlights the importance of timing, dosing, and selecting the right patient or tumour subtype.

Clinical trials are underway: FAP vaccines with chemotherapy, CXCR4 inhibitors with PD-1 blockers, and Hedgehog inhibitors with chemotherapy are being tested [140]. A future direction is personalized stromal therapy based on CAF activity. For instance, tumours with high IL-6/STAT3 activity might benefit from IL-6 or JAK/STAT3 inhibitors, while those rich in hyaluronan could respond to PEGPH20 or collagen synthesis inhibitors [141, 142]. Characterizing CAF profiles via biopsy or FAP-targeted PET imaging could guide tailored interventions [143]. In sum, reprogramming, depleting, or blocking specific CAF subsets holds great potential for overcoming resistance and improving therapeutic efficacy.

Conclusion and future perspectives

Cancer-associated fibroblasts (CAFs) centrally reinforce cancer hallmarks and materially shape therapeutic resistance. Crucially, their heterogeneity is a double-edged sword: certain subsets accelerate progression, whereas others may restrain it. Moving beyond bulk stroma views, future efforts should prioritize subtype-resolved characterization—leveraging single-cell and spatial profiling—to enable precision anti-CAF strategies. Current data delineate actionable classes with distinct secretomes and niches, including contractile myCAFs (ECM/solid-stress; drug-penetration barriers), inflammatory iCAFs (IL-6/chemokines; STAT3-driven stemness), antigen-presenting-like apCAFs (MHC-II; T-cell dysfunction),

metabolically active meCAFs (nutrient/ROS buffering), lipid-laden CAFs (angiogenic remodeling), and senescent/SASP CAFs (post-therapy relapse) (Table 1). These patterns argue for selective modulation rather than pan-depletion. Clinically, patients with IL-6^{high} iCAFs may benefit from JAK/STAT3 inhibitors [144], whereas FAP^{+}myCAF-rich stroma could be addressed with FAP-targeted or stroma-normalizing approaches (e.g., FAK/LOX pathway or vitamin-D analogues). Prospective trials should integrate spatial biomarkers for enrolment and longitudinal monitoring to match CAF programs with the right combinatorial regimens.

Technological advances such as single-cell multi-omics and 3D co-culture organoid models incorporating CAFs and immune cells are transforming our understanding of CAF function and drug response. These platforms offer a preclinical avenue to tailor tumour-stroma combination therapies before clinical application. CAF-directed imaging tools, like FAP-targeted PET tracers, are being explored to visualize stromal activity and monitor treatment responses [143]. Some researchers are even investigating therapeutic uses of CAFs, for example, engineering T cells or viruses to home in on CAF-rich areas, or using CAFs as drug delivery vehicles.

Clinically, combining stromal modulation with immunotherapy or chemotherapy has shown promise, especially in difficult cancers like PDAC and liver cancer. Past setbacks (e.g., MMP inhibitors) have highlighted the need for timing, patient selection, and multi-targeted strategies. More refined approaches—such as transient CAF modulation or combined pathway targeting—are likely to shape future trials.

In conclusion, targeting CAFs offers a promising strategy to dismantle the tumour-supportive ecosystem. A shift from tumour-centric to ecosystem-based therapies could yield deeper, more durable responses. CAFs, as central enablers of resistance, must be considered in any comprehensive therapeutic strategy. Continued exploration into CAF biology will be key to advancing cancer treatment.

Abbreviations

ATRA	All-trans retinoic acid
apCAF	Antigen-presenting CAF
CSC	Cancer stem cell
CAF	Cancer-associated fibroblast
CRC	Colorectal cancer
CTL	Cytotoxic T lymphocyte
ECM	Extracellular matrix
EV	Extracellular vesicle
FAP	Fibroblast activation protein
FGF	Fibroblast growth factor
GBC	Gallbladder cancer
HNSCC	Head and neck squamous cell carcinoma
HCC	Hepatocellular carcinoma
iCAF	Inflammatory and growth factor-enriched CAF
IL	Interleukin
MSC	Mesenchymal stem cell
myCAF	Myofibroblastic CAF
NSCLC	Non-small cell lung cancer
PC	Pancreatic cancer
PDAC	Pancreatic ductal adenocarcinoma
PDGF	Platelet-derived growth factor
RCC	Renal cell carcinoma
TSG-6	TNF-stimulated factor 6
TGF-β	Transforming growth factor-β
TME	Tumour microenvironment
TNT	Tunnelling nanotube
VDR	Vitamin D receptor
α-SMA	α-smooth muscle actin

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Authors' contributions
Ning Wang conceived the overall idea and finalized the manuscript. Yuanjun Lu drafted the whole manuscript and prepared figures and tables. Ya Wu and Xiaoyu Xu collected the data and organized tables. Yibin Feng revised the manuscript. All authors approved the final manuscript.

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