

Emerging agents that target signaling pathways in cancer fibroblast cells (Review)

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Abstract. Cancer-associated fibroblasts (CAFs) play a critical role in cancer development, recurrence and metastasis. Several signaling pathways are crucial in CAF development, including fibroblast activation protein (FAP), phosphoinositide 3-kinase (PI3K)/protein kinase B (AKT)/mechanistic target of rapamycin (mTOR), Janus kinase/signal transducers and activators of transcription (JAK/STAT), nuclear factor κ B (NF- κ B), transforming growth factor β (TGF- β), ferroptosis, apoptosis and autophagy pathways. Targeting the ferroptosis signaling pathway specifically kills CAFs. Therefore, targeting these pathways may inhibit the protumorigenic functions of CAFs. Small molecule drugs, due to their well-dispersed spatial structures and distinct chemical properties, exhibit promising druggability and pharmacokinetic profiles. These characteristics make small molecule drugs highly advantageous in drug development and increasingly favored in the market. The present review summarized current studies on small molecule compounds that inhibit CAF progression, encompassing inhibitors of the PI3K/AKT/mTOR, JAK/STAT, TGF- β and NF- κ B pathways, as well as activators of the FAP, ferroptosis, apoptosis and autophagy pathways. These small molecule compounds underscore the significance of CAFs in tumor progression and suggest novel strategies for cancer treatment by targeting CAFs in clinical settings.

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1. Introduction

Cancer remains a leading cause of mortality worldwide, with the World Health Organization reporting nearly 10 million deaths in 2020, accounting for ~1 in 6 fatalities globally (1). Despite the efficacy of conventional therapies in markedly reducing tumor burden, recurrence and metastasis frequently occur, ultimately resulting in treatment failure. A major factor contributing to this failure is the inadequate consideration or neglect of the tumor microenvironment (TME) in antitumor strategies (2). The TME comprises various immune cell populations, cancer-associated fibroblasts (CAFs), endothelial cells, pericytes and a diverse array of other tissue-resident cell types. Historically regarded as passive bystanders in tumorigenesis, these host cells are now recognized as critical players in cancer pathogenesis. The cellular composition and functional states of the TME vary markedly depending on the organ of tumor origin, intrinsic characteristics of cancer cells, tumor stage and patient-specific factors (3). Among TME components, CAFs are pivotal in cancer initiation and progression, owing to their multifaceted roles in extracellular matrix (ECM) remodeling, maintenance of stemness properties, angiogenesis, modulation of tumor metabolism and immune responses, as well as their promotion of cancer cell proliferation, migration, invasion and therapeutic resistance. CAFs represent a highly heterogeneous stromal population, engaging in complex and intricate crosstalk with cancer cells mediated by an array of signaling pathways, including transforming growth factor- β (TGF- β), phosphatidylinositol 3-kinase (PI3K)/protein kinase B (AKT)/mammalian target of rapamycin (mTOR), mitogen-activated protein kinase (MAPK), Wnt, Janus kinase (JAK)/signal transducer and activator of transcription (STAT), epidermal growth factor receptor (EGFR), Hippo and nuclear factor κ B (NF- κ B) pathways. These signaling cascades give rise to distinct CAF phenotypes during tumor progression and represent promising targets for anticancer therapy (4).

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Furthermore, fibroblasts display phenotypic plasticity influenced by their microenvironmental context. Activated fibroblasts within tumors are termed CAFs (5,6). Distinct from normal fibroblasts, CAFs exhibit differential expression of markers such as α -smooth muscle actin (α -SMA), fibroblast activation protein (FAP), fibroblast-specific protein 1 and platelet-derived growth factor receptor (PDGFR) (7). In addition to these, proteins including collagen type XI α 1 chain (COL11A1), microfibril-associated protein 5 and asporin are predominantly expressed in CAFs (8,9). The concept of intratumoral CAF heterogeneity recognizes the existence of distinct CAF subsets, such as inflammatory CAFs characterized by low α -SMA and high interleukin-6 (IL-6) expression, contrasting with TGF- β -dependent myofibroblastic CAFs exhibiting high α -SMA levels (10).

A novel therapeutic approach targeting CAFs is the 'stromal reprogramming' strategy, which aims to convert tumor-promoting CAFs into tumor-inhibitory phenotypes by reducing matrix stiffness (11). Despite recent advances, several molecular mechanisms underpinning CAF biology remain to be fully elucidated, posing challenges to the development of personalized anticancer therapies targeting the stroma. Accordingly, strategies that concurrently address both the tumor stroma and cancer cells have garnered considerable attention in the context of precision oncology. Collectively, CAFs constitute a predominant cellular component within the TME and play a pivotal role in regulating tumor biological behavior (12). However, most current tumor therapies primarily target the proliferative tumor cells and exert limited effects on CAFs. This therapeutic gap partially explains why reductions in tumor volume do not invariably translate into improved patient survival outcomes.

Due to their diverse origins and complex activation mechanisms, CAFs are recognized as critical modulators of tumorigenesis, tumor progression and therapeutic resistance (13). Consequently, specific interventions targeting CAFs hold promise for enhancing anticancer efficacy and their combination with conventional therapies may potentially achieve curative results. The biological functions of CAFs are orchestrated by various intracellular and extracellular factors, notably signaling pathways intimately involved in cancer progression, which present viable targets for therapeutic intervention. Currently, signaling cascades including FAP, PI3K/AKT/mTOR, JAK/STAT, NF- κ B and TGF- β , as well as pathways regulating ferroptosis, apoptosis and autophagy, are extensively investigated for mediating the crosstalk between CAFs and cancer cells, thereby serving as potential targets for cancer therapy (14).

Of particular interest, the induction of ferroptosis, apoptosis and autophagy in CAFs has recently emerged as a novel mechanistic approach, demonstrating promising therapeutic potential (15). Integrating conventional treatments such as chemotherapy or radiotherapy with CAFs-targeted agents may result in improved inhibition of tumor initiation, growth, progression, recurrence and metastasis. The present review summarized the current landscape of small-molecule compounds that suppress CAF activity, focusing on inhibitors of the PI3K/AKT/mTOR, JAK/STAT, TGF- β , ferroptosis and autophagy pathways, as well as activators of apoptotic signaling. These insights may provide a valuable foundation

for the development of enhanced therapeutic strategies in cancer management.

2. Signaling pathway regulators

CAF, a major component of the TME, have been found to be involved in various cellular processes. Their biological activity is mediated by multiple intracellular and extracellular factors, particularly cancer-associated signaling cascades, which may serve as targets for anticancer therapy. Among these signaling pathways, PI3K/AKT/mTOR, JAK/STAT, NF- κ B and TGF- β (14) have been extensively studied for the development of new drugs targeting CAFs (Fig. 1).

PI3K/AKT/mTOR signaling pathway inhibitors. The PI3K/AKT/mTOR signaling pathway is intimately involved in multiple facets of cancer biology, including the proliferation, differentiation, growth, apoptosis and migration of CAFs (16). PI3K consists of a regulatory subunit (p85) and a catalytic subunit (p110). Upon engagement with growth factor receptors such as EGFR, PI3K undergoes conformational changes that lead to the activation of Akt. Activated Akt subsequently phosphorylates downstream substrates, including apoptosis-related proteins Bad and Caspase-9, thereby modulating cellular processes such as proliferation, differentiation, apoptosis and migration. The mTOR, a key downstream effector of the PI3K/Akt pathway, is activated when Akt directly phosphorylates its Ser1448 residue. Activation of mTOR and its downstream signaling cascades regulates the translation of specific proteins essential for cell proliferation and transformation (17). The PI3K/AKT pathway has a critical role in CAF proliferation (Fig. 2), which is often driven by oxidative stress; a fundamental contributor to aberrant CAF expansion. Ataxia-telangiectasia mutated protein kinase, a pivotal redox sensor, is induced by PI3K/AKT pathway activation, thereby promoting the abnormal proliferation of breast CAFs (18). Furthermore, accumulating evidence indicates that the PI3K/AKT signaling axis facilitates the differentiation of various precursor cell types into CAFs. For instance, exosomes derived from gastric cancer cells induce the transdifferentiation of pericytes into CAFs via activation of the PI3K/AKT pathway (19). Additionally, hepatocellular carcinoma (HCC)-derived exosomal micro (mi) RNA-21 transforms hepatic stellate cells into CAFs through the Akt signaling pathway (20). Additionally, osteosarcoma cells stimulate the differentiation of mesenchymal stem cells into CAFs through Akt-dependent pathways, evidenced by increased expression of the CAF marker α -SMA (21). Given these roles, targeting components of the PI3K/AKT pathway represents a promising therapeutic strategy to inhibit the function of CAFs. Multiple studies have demonstrated that inhibitors targeting the PI3K/AKT/mTOR axis, whether administered alone or in combination with chemotherapeutic agents, effectively suppress CAF activity and consequently impede tumor progression (Table I) (22-35).

For example, the combination treatment of dovitinib with the PI3K/AKT/mTOR signaling inhibitors LY294002 or RAD001 resulted in additive inhibition of CAF invasion, demonstrating therapeutic activity against breast cancer metastasis (22). Rocuronium bromide, a non-depolarizing neuromuscular blocker, has been shown to inhibit the PI3K/

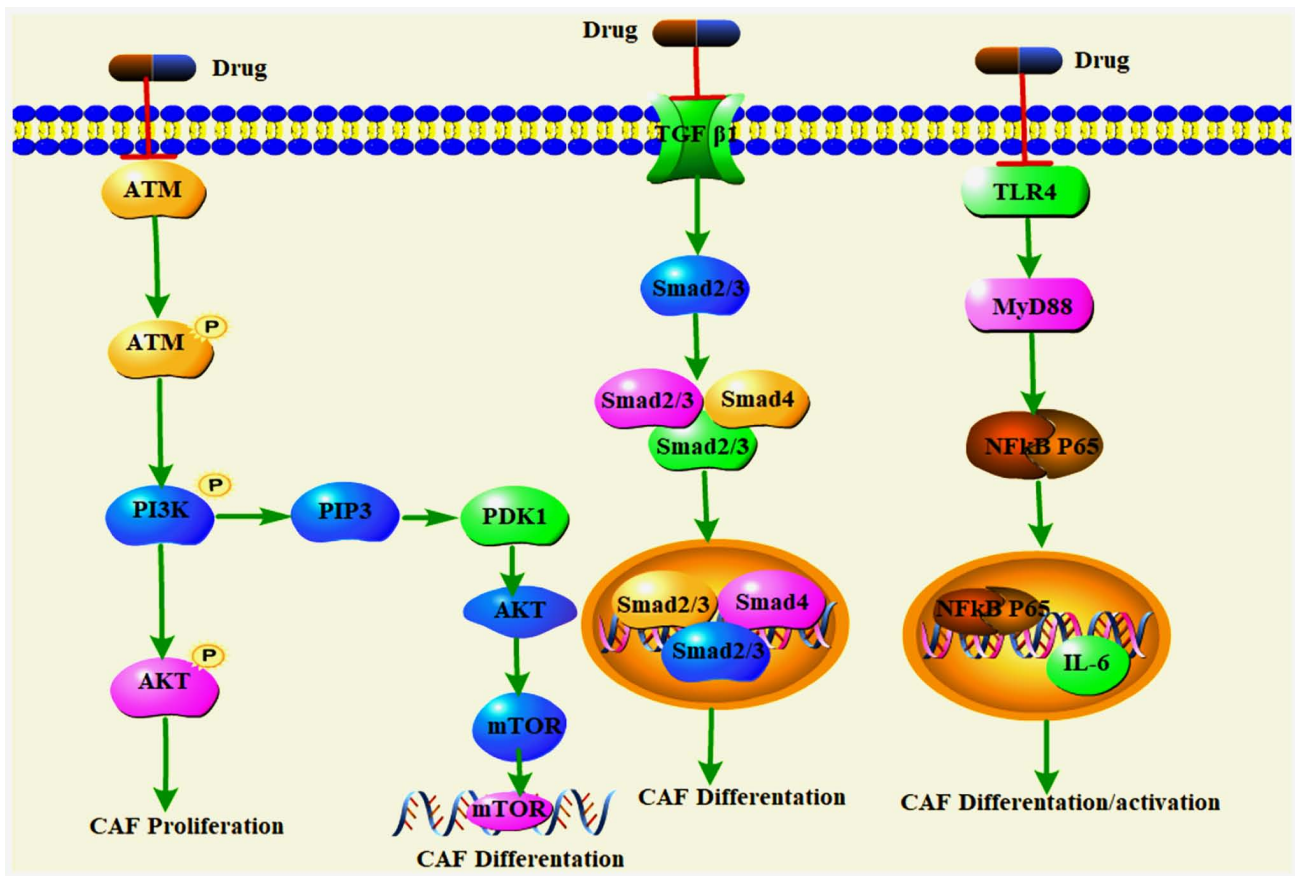


Figure 1. Small molecule agents inhibit the proliferation, differentiation and activation of CAFs by inhibiting PI3K/AKT/mTOR signaling pathways, TGF- β pathway and NF- κ B. CAFs, cancer-associated fibroblasts; PI3K, phosphatidylinositol 3-kinase; AKT, protein kinase B; mTOR, mechanistic target of rapamycin; TGF- β , transforming growth factor β ; NF- κ B, nuclear factor κ B; ATM, ataxia telangiectasia-mutated; PIP3, phosphatidylinositol 3 trisphosphate; PDK1, pyruvate dehydrogenase kinase 1; SMAD, mothers against DPP homolog; TLR4, Toll-like receptors 4; MyD88, myeloid differentiation primary response 88; IL-6, interleukin-6.

AKT/mTOR signaling pathway, thereby blocking CAFs and attenuating esophageal cancer progression (23). Oxaliplatin, a classic third-generation platinum-based chemotherapeutic agent, inhibits xenograft tumor growth in mouse xenograft models by targeting the C-X-C chemokine motif receptor 3 (CXCR3)/PI3K/AKT axis secreted by CAFs (24).

The classic Chinese medicine formula Biejiajian pill has been found to inhibit HCC progression by suppressing PI3K and AKT phosphorylation in a mouse model of diethylnitrosamine/carbon tetrachloride-induced HCC (25). Inhibition of AKT phosphorylation is a key strategy to target CAFs. For instance, cisplatin, a commonly used anticancer drug, has been shown to reduce the ability of CAFs to promote lung cancer cell migration and invasion by inhibiting the AKT signaling pathway both in tumor cell models and in BALB/c nude mice tumor models (26). Cisplatin inadvertently induces CAFs to secrete plasminogen activator inhibitor-1 (PAI-1) and this paracrine cue fosters tumor progression while diminishing cisplatin response. Targeting PAI-1 with Tiplaxtinin inhibits AKT activation in CAFs and enhances cisplatin efficacy, producing *in vitro* and *in vivo* synergy (27).

Similarly, gold nanoparticles can enhance the effects of cisplatin by decreasing the density of CAFs through the Akt signaling pathway and reducing collagen I production in colorectal cancer (CRC) xenograft mice (28). Furthermore, the combination of camatinib and osimertinib markedly enhances tumor

suppression and decreases CAF abundance in patient-derived xenograft models via AKT pathway inhibition in non-small cell lung cancer (NSCLC) (29). Mesalazine and the mTOR inhibitor everolimus, originally developed as immunosuppressants to prevent organ rejection, have recently been found to exert anti-proliferative effects on cholangiocarcinoma cells by blocking CAF-activated AKT signaling (30). Regorafenib, a multikinase inhibitor, has been shown to inhibit proliferation and induce apoptosis in CAFs *in vitro*, with its mechanism linked to the inhibition of AKT phosphorylation (31).

In NSCLC models, anlotinib was demonstrated to modulate the TME by inhibiting the AKT pathway and promoting CAF apoptosis, thereby enhancing therapeutic efficacy against NSCLC (32). Furthermore, bioactive compounds isolated from commonly consumed beverages exhibit CAF-inhibitory effects via AKT suppression. For instance, caffeine (1,3,7-trimethylxanthine), the most widely consumed psychoactive substance worldwide, inhibits CAF migration and invasion through phosphatase and tensin homolog-dependent inactivation of Akt and Erk1/2 signaling, effectively preventing breast tumor growth and recurrence in a safe manner (33). Dihydromyricetin, a flavonoid that is the main active ingredient in *Garcinia cambogia*, has been found to inhibit the proliferative potential of CAFs by targeting Akt activation (34). Additionally, researchers synthesized a drug targeting mTOR, tetracyclic heterocyclic azathiophenone MSI-N1014, which was able to inhibit the

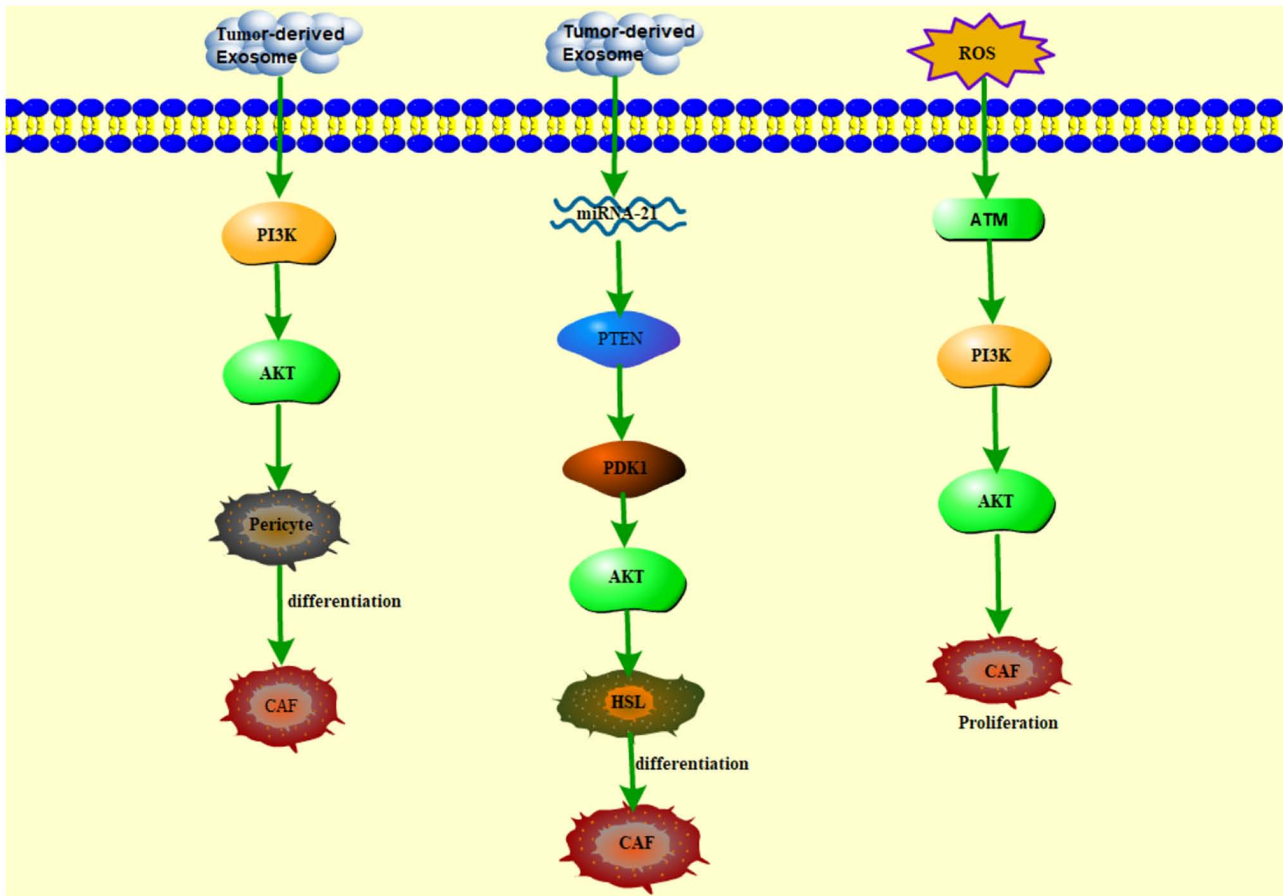


Figure 2. Tumor-derived exosomes and oxidative stress environment promote CAFs proliferation and differentiation through the PI3K/AKT/mTOR pathway. CAFs, cancer-associated fibroblasts; PI3K, phosphatidylinositol 3-kinase; AKT, protein kinase B; mTOR, mechanistic target of rapamycin; ATM, ataxia telangiectasia-mutated genataxia telangiectasia-mutated; PIP3, phosphatidylinositol 3trisphosphate; PTEN, phosphatase and tensin homolog; PDK1, pyruvate dehydrogenase kinase 1.

transformation of CAFs by decreasing mTOR expression, thus markedly reducing migratory ability, tumor-ballooning generation and resistance to 5-fluorouracil (35).

In conclusion, current studies on regulating CAFs by inhibiting the PI3K/AKT/mTOR pathway primarily focus on suppressing the functions and activities of CAFs through this pathway. These include inhibiting CAF proliferation, promoting CAF apoptosis and reducing the secretion of pro-tumorigenic factors by CAFs. Most approaches utilize small molecule inhibitors or genetic interventions, indicating the critical role of the PI3K/AKT/mTOR signaling in modulating CAF activity. However, given the broad involvement of this pathway in diverse cellular processes, highly selective interventions targeting CAFs specifically are still lacking and treatment often carries significant systemic side effects. Overall, among the strategies targeting CAFs via the PI3K/AKT/mTOR pathway, the application of small molecule inhibitors is the most mature and has demonstrated considerable efficacy in suppressing CAF function. Nevertheless, these approaches predominantly focus on direct depletion or inactivation of CAFs, with relatively limited emphasis on stromal reprogramming. A subset of studies aiming for selective blockade of specific PI3K isoforms or downstream effectors has shown promising improvements in CAF selectivity, suggesting potential advantages. Furthermore, strategies

that induce stromal remodeling through modulation of this pathway remain in the early stages of investigation; combining pathway inhibition with stromal reprogramming could yield more durable therapeutic outcomes in the future. In terms of clinical translation, most research remains at the preclinical stage, lacking comprehensive clinical validation and safety evaluation. Future efforts should prioritize the development of highly selective PI3K/AKT/mTOR modulators in conjunction with multimodal treatment strategies to optimize CAF-targeted therapies, ultimately achieving more effective antitumor responses with reduced off-target toxicity.

JAK-STAT signaling pathway inhibitors. The JAK-STAT signaling pathway consists of three components: The tyrosine kinase-associated receptor that receives the signal, the tyrosine kinase JAK that transmits the signal and the transcription factor STAT that produces the effect. When various cytokines or growth factors bind to receptors, they phosphorylate and activate JAK. JAK then phosphorylates tyrosine residues on downstream target proteins and recruits and phosphorylates the transcription factor STAT (36). STAT forms dimers and enters the nucleus, where it binds to target genes and regulates their transcription. This process influences cell proliferation, differentiation and apoptosis (37). The JAK/STAT signaling pathway is constitutively activated in CAFs. For instance,

Table I. Small-molecule compounds inhibiting CAF-induced cancer through suppressing PI3K/AKT/mTOR signaling pathways.

First author/s, year	Name	Target	Type of cancer	Study type	Anticancer mechanisms	(Refs.)
Zhang, 2015	Dovitinib with LY294002 or RAD001	PI3K/AKT/mTOR	Breast cancer	Preclinical	Inhibited CAF invasion	(22)
Li, 2023	Rocuronium	PI3K/AKT/mTOR	Esophageal cancer	Preclinical	Inhibited CAF secretion of the pro-tumor cytokine CXCL12	(23)
Lu and Zhang, 2023	Oxaliplatin	CXCR3/PI3K/AKT	Colorectal cancer	Preclinical	Reduced cancer cell proliferation	(24)
Chen, 2023	Biejiajian pill	PI3K/AKT	Hepatocellular carcinoma	Preclinical	Reduced expression of VEGF-A and HGF by CAF	(25)
Li, 2020	Cisplatin	AKT	Lung cancer	Preclinical	Attenuated CAF metastasis-promoting effects	(26)
Che, 2018	Tiplaxtinin	AKT	Esophageal squamous cell carcinoma	Preclinical	Inhibited tumor growth and improved CAF-induced tumor microenvironment	(27)
Zhao, 2018	Gold nanoparticles	AKT	Colorectal cancer	Preclinical	Enhanced cisplatin delivery and decompression of cancer vessels	(28)
Zhu, 2021	Capmatinib	AKT	NSCLC	Preclinical	Reduced production of CAF	(29)
Heits, 2016	Mycophenolic acid and Everolimus	mTOR; AKT	Cholangiocellular carcinoma	Preclinical	Reduced migration and invasive activity of CAF	(30)
Zhang, 2022	Regorafenib	AKT	Gastrointestinal cancer	Preclinical	Induced apoptosis in gastrointestinal CAF	(31)
Tang, 2024	Anlotinib	AKT	NSCLC	Preclinical	Promoted CAF apoptosis	(32)
Al-Ansari and Aboussekhra, 2014	Caffeine	AKT	Breast cancer	Preclinical	Induced sustained inactivation of breast CAF	(33)
Fan, 2017	Dihydromyricetin	AKT	Lung cancer	Preclinical	Inhibited proliferation of lung CAF	(34)
Yadav, 2020	MSI-N1014	mTOR	Colorectal cancer	Preclinical	Reduced conversion of cancer cells to CAF	(35)

CAFs, cancer-associated fibroblasts; PI3K, phosphatidylinositol 3-kinase; AKT, protein kinase B; mTOR, mechanistic target of rapamycin; NSCLC, non-small cell lung cancer.

CAFs can promote endometrial cancer growth by inducing the IL-6-activated STAT-3 pathway (38).

Similarly, in prostate cancer, CAF-derived IL-6 can attenuate p53 activity by activating the JAK/STAT signaling pathway, thereby protecting cancer cells from chemotherapy (39). Furthermore, in pancreatic ductal adenocarcinoma (PDAC), activation of the JAK/STAT signaling pathway induced by IL-1 also produces inflammatory CAFs, which promote tumor growth (40). In summary, CAF-induced

cytokines activate the JAK/STAT signaling pathway and the activated JAK/STAT signaling pathway in turn produces more CAFs, ultimately promoting tumorigenesis and progression. Therefore, inhibition of the JAK2/STAT3 signaling pathway may be a crucial strategy to suppress cancer stemness, plasticity and intercellular signaling between CAFs and cancer cells (Table II) (41-49).

Bufalin, the main active monomer of the clinical drug cinobufacini, has garnered increasing attention for its antitumor

Table II. Small-molecule compounds inhibiting CAF-induced cancer through suppressing JAK-STAT signaling pathways.

First author/s, year	Name	Target	Type of cancer	Study type	Anticancer mechanisms	(Refs.)
Wang, 2023	Bufalin	STAT3	Colorectal cancer	Preclinical	Reversed CAF-mediated cancer invasion and metastasis	(41)
Ochi, 2022	Tranilast	STAT3	Non-small cell lung cancer	Preclinical	Reversed CAF resistance to molecularly targeted drugs	(42)
Al-Jomah, 2021	Tocilizumab	STAT3	Breast cancer	Preclinical	Inhibited proliferation, migration and invasive capacity of activated breast CAF	(43)
Ham, 2022	Curcumin	JAK/STAT3	Gastric cancer	Preclinical	Counteracted CAF-induced chemotherapy resistance	(44)
Cao, 2020	Oroxlylin A	STAT3	Breast cancer	Preclinical	Prevented the activation of CAF	(45)
Suh, 2018	Resveratrol	STAT3	Breast cancer	Preclinical	Inhibited CAF-induced migration, invasion and self-renewal activity of breast cancer cells	(46)
Tsang, 2013	Berberine	STAT3	Nasopharyngeal carcinoma	Preclinical	Regulated the CAF-induced inflammatory tumor microenvironment	(47)
Zhang, 2023	<i>Lentinus edodes</i> polysaccharide	JAK2/STAT3	Prostate cancer	Preclinical	Inhibited CAF-induced drug resistance	(48)
Lee, 2020	β -Carotene	STAT3	Colorectal cancer	Preclinical	Prevented the activation of CAFs	(49)

CAFs, cancer-associated fibroblasts; JAK, Janus kinase; STAT, signal transducers and activators of transcription.

activity in various cancers. Research has shown that bufalin can reverse CAF-mediated CRC metastasis by inhibiting the STAT3 signaling pathway (41). Trinilast, an anti-allergic drug that inhibits cytokine release in various inflammatory cells, was recently found to reverse CAF-mediated resistance of NSCLC cells to molecularly targeted drugs both *in vitro* and *in vivo* when co-administered with molecularly targeted therapy. This effect is related to the inhibition of CAF-induced upregulation of phosphorylated STAT by trinilast (42). Tocilizumab, a recombinant humanized monoclonal antibody approved by the Food and Drug Administration (FDA) for treating various immune disorders, normalizes active breast CAFs and inhibits their paracrine pro-oncogenic effects by blocking the STAT3 pathway (43).

Curcumin, extracted from the root of the herb turmeric, has been found to inhibit CAF-mediated activation of the JAK/STAT3 signaling pathway, thereby overcoming chemoresistance (44). Additionally, Oroxlylin A and resveratrol, both extracted from herbs, have been shown to prevent CAF activation by inhibiting STAT3 phosphorylation (45,46). Similarly, berberine, another compound extracted from Chinese herbs,

effectively inhibited CAF-induced STAT3 activation, thereby suppressing the tumorigenicity and growth of nasopharyngeal carcinoma cells (45). A novel mushroom polysaccharide, MPSSS, extracted from food, was shown to be an adjuvant treatment for prostate cancer by inhibiting the JAK2/STAT3 pathway in CAFs (48). β -Carotene, isolated from carrots, inhibited CAF activation by suppressing the IL-6/STAT3 signaling pathway, thus demonstrating its therapeutic potential in cancer progression and metastasis (49).

Current research targeting CAFs through inhibition of the JAK-STAT signaling pathway not only focuses on suppressing CAF activity and function but also addresses overcoming CAF-driven drug resistance and modulating tumor stromal remodeling. Representative agents include Oroxlylin A, Resveratrol and Berberine; however, these interventions generally lack high specificity toward CAFs, limiting therapeutic precision and potentially causing off-target effects. Most studies remain at the preclinical stage, providing foundational insights for future clinical translation. Among these approaches, small molecule natural compounds are the most mature, demonstrating effectiveness in inhibiting CAF

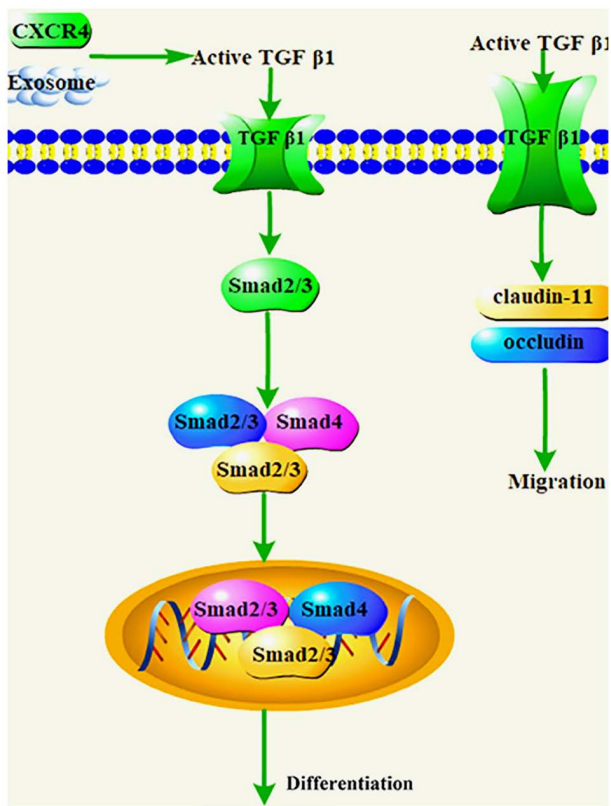


Figure 3. Activation of the TGF- β signaling pathway promotes CAF migration and differentiation. TGF- β , transforming growth factor β ; CAFs, cancer-associated fibroblasts; CXCR4, C-X-C motif chemokine receptor 4; SMAD, mothers against DPP homolog.

activation and reversing resistance mechanisms. Importantly, some evidence indicates that such treatments do not merely deplete CAF populations but also induce functional reprogramming of the tumor stroma, broadening therapeutic possibilities. From a translational perspective, these strategies are still in their infancy, highlighting the need to develop more selective JAK-STAT modulators targeting CAFs and prioritize therapies promoting stromal remodeling rather than simple elimination of CAFs, thereby facilitating the safe and effective transition of preclinical findings into clinical applications.

TGF- β signaling pathway inhibitors. The TGF- β signaling pathway is a superfamily of structurally related multifunctional cytokines, including TGF- β proteins, activins, inhibins, bone morphogenetic proteins (BMPs) and growth and differentiation factors. TGF- β signaling is closely associated with CAF activation or transformation (Fig. 3). For example, bladder cancer cell-derived exosomes have been found to induce the differentiation of fibroblasts into CAFs via TGF- β signaling (50). Similarly, hepatic stellate cells can differentiate into CAFs through the activation of the TGF- β 1 signaling pathway, promoting liver metastasis in colon cancer (51). In ovarian cancer, COL11A1 promotes tumor formation and CAF activation through the activation of the TGF- β 3 signaling pathway (52). Additionally, the prostate cancer microenvironment can recruit and differentiate mesenchymal stromal cells into CAFs via TGF- β 1 (53). Activation of TGF- β signaling is also associated with CAF migration. Evidence suggests that

TGF- β signaling activation promotes the collective migration of CAFs by overexpressing tight junction-associated proteins claudin-11 and occludin (54). Furthermore, the CAF-mediated TGF- β pathway promotes cancer progression by regulating cancer cell proliferation, migration, invasion and metastasis (55). Overall, TGF- β signaling and CAFs complement each other: TGF- β signaling influences CAF activity, while CAFs promote cancer progression through TGF- β signaling. Therefore, targeted inhibition of the TGF- β signaling pathway may be an effective strategy to suppress cancer progression and CAFs activation (Table III) (56-79).

Eribulin is a well-tolerated anti-microtubule drug used to treat various tumors. It has been found to ‘normalize’ CAF function in pancreatic CAFs by a mechanism similar to blocking the TGF- β -induced pathway, suggesting that Eribulin could be used as a CAFs/stromal standardizing drug (56). Preclinical studies reported a self-assembled nanoplatform of hyaluronic acid (HA)-paclitaxel (PTX) (HA-PTX) prodrugs and Marimastat (MATT)-loaded thermosensitive liposomes (LTSLS; MATT-LTSLS) for the treatment of metastatic cancers by downregulating TGF- β expression and blocking CAF activation (57).

Similarly, the TGF- β R1 inhibitor Galunisertib (LY2157299) monohydrate inhibited tumor growth in ovarian cancer by blocking fibroblast activation through downregulation of TGF- β expression (58). Of note, TGF- β 1 induced the formation of CAF phenotypes in starved NIH3T3 fibroblasts and xenografted Balb/c mice, thereby promoting breast cancer tumor growth. By contrast, blockade of TGF- β 1 induced these effects following the administration of the TGF- β type I receptor kinase inhibitor LY-2157299 (59).

Sulfosuccinimidyl oleate sodium, a CD3 inhibitor, was found to have a significant negative effect on the proliferative and migratory capacity of CAFs and further mechanistic studies were found to be associated with a reduction in the levels of related activation genes (α -SMA, FAP and waveform protein) and cytokines (IL-6, TGF- β and VEGF- α) in nude mice orthotopically implanted with CAFs and HCC cells (60).

The combination of non-steroidal anti-inflammatory drugs (aspirin and ibuprofen) with vincristine effectively inhibited the secretion of TGF- β and IL-6 from CAFs in CRC, thereby reducing chemoresistance to vincristine (61).

Metformin (Met), a first-line drug for diabetes treatment, can disrupt tumor-stromal crosstalk by blocking TGF- β signaling in breast cancer cells (62). Additionally, the cardiac glycoside analog digoxin is a particularly potent CAF blocker, capable of inhibiting TGF- β -induced fibronectin expression at low nanomolar concentrations without causing cytotoxicity (63).

Pirfenidone, an antifibrotic agent and TGF- β antagonist, synergizes with adriamycin to inhibit triple-negative breast cancer by inducing apoptosis in CAFs cells and suppressing CAF proliferation through inhibiting TGF- β expression (64). Furthermore, pirfenidone induces apoptosis in lung CAF cells by inhibiting TGF- β 1 (65). Another TGF- β receptor inhibitor, LY2109761, was found to disrupt the crosstalk between cancer cells and CAFs by inhibiting TGF- β expression, leading to a significant reduction in HCC growth and dissemination (66).

Meanwhile, Halofuginone, an old antiparasitic drug for poultry, has been found to inhibit the TGF- β /Smad2/3

Table III. Small-molecule compounds inhibiting CAF-induced cancer through suppressing TGF- β signaling pathways.

First author/s, year	Name	Target	Type of cancer	Study type	Anticancer mechanisms	(Refs.)
Luong and Cukierman, 2022	Eribulin	TGF- β	Pancreatic cancer	Preclinical	Normalized pancreatic CAFs	(56)
Lv, 2018	HA-PTX/MATT-LTSLs HNPs	TGF- β 1	Breast cancer	Preclinical	Blocked CAF activation	(57)
Zhang, 2018	LY2157299 monohydrate	TGF- β 1	Ovarian cancer	Preclinical	Blocked CAF activation	(58)
Liu, 2016	LY2157299	TGF- β 1	Breast cancer	Preclinical	Inhibited the formation of CAFs	(59)
Wang, 2024	Sulfosuccinimidyl oleate sodium	TGF- β 1	Hepatocellular carcinoma	Preclinical	Inhibited CAF proliferation	(60)
Wawro, 2019	Aspirin and ibuprofen	TGF- β s	Colon cancer	Preclinical	Inhibited the formation of CAFs	(61)
Shao, 2020	Metformin	TGF- β	Breast cancer	Preclinical	Inhibited tumor invasion	(62)
Coleman, 2016	Digoxin	TGF- β	Others	Preclinical	Inhibited differentiation of CAFs	(63)
Takai, 2016	Pirfenidone	TGF- β	Breast cancer	Preclinical	Delayed transdifferentiation of fibroblasts to CAFs	(64)
Mediavilla-Varela, 2016	Pirfenidone	TGF- β 1	Non-small cell lung cancer	Preclinical	Killed CAFs	(65)
Mazzocca, 2010	LY2109761	TGF- β	Hepatocellular carcinoma	Preclinical	Inhibited CAF proliferation	(66)
Wang, 2022	Halofuginone	TGF- β	Oral squamous cell carcinoma	Preclinical	Inhibited CAF proliferation	(67)
Gabasa, 2017	Nintedanib	TGF- β 1	Lung adenocarcinoma	Preclinical	Blocked CAF activation	(68)
Shangguan, 2012	Bone morphogenetic protein and activin membrane-bound inhibitor	TGF- β	Others	Preclinical	Blocked differentiation of human mesenchymal stem cells to CAFs	(69)
Yao, 2019	Artemisinin derivatives	TGF- β	Breast cancer	Preclinical	Blocked CAF activation	(70)
Milián, 2022	Δ 9-Tetrahydrocannabinol and Cannabidiol	TGF- β	Lung cancer	Preclinical	Inhibited CAF proliferation	(71)
Melegová, 2022	<i>Aesculus hippocastanum</i> L. extract	TGF- β 1	Basal cell carcinoma; squamous cell carcinoma	Preclinical	Improved CAF-induced tumor microenvironment	(72)
Buhrmann, 2014	Curcumin	TGF- β	Colon cancer	Preclinical	Improved CAF-induced tumor microenvironment	(73)
Liang, 2023	Chelerythrine chloride	TGF- β 2	Colon cancer	Preclinical	Blocked CAF activation	(74)
Jalilian, 2023	Curcumin	TGF- β	Breast cancer	Preclinical	Inhibited the CAF phenotype	(75)
Ting, 2016	Silibinin	TGF- β 2	Prostate cancer	Preclinical	Blocked CAF activation	(76)
Ting, 2015	Silibinin	TGF- β 2	Prostate cancer	Preclinical	Prevented prostate cancer cell-mediated differentiation of naive fibroblasts into CAFs	(77)

Table III. Continued.

First author/s, year	Name	Target	Type of cancer	Study type	Anticancer mechanisms	(Refs.)
Jin, 2023	Baicalein-loaded mPEG-PLGA nanoparticles	TGF- β	Breast cancer	Preclinical	Blocked CAF activation	(78)
Pang, 2024	The TGF- β receptor I inhibitor SB525334 (SB) and docetaxel micelles	TGF- β	Pancreatic cancer	Preclinical	Suppresses the activity of myofibroblastic CAFs	(79)

CAFs, cancer-associated fibroblasts; TGF- β , transforming growth factor β .

signaling pathway, thereby attenuating the promotional effect of CAFs on the migration and invasion of oral squamous cell carcinoma (OSCC) cells (67). Similarly, Nintedanib, a clinically approved multikinase receptor inhibitor, has been found to inhibit TGF- β 1-induced expression of a panel of pro-fibrotic activation markers in adenocarcinoma CAFs (68). Additionally, some investigators have used lentiviral vectors encoding BMPs and activin membrane-bound inhibitor to inhibit TGF- β /Smad signaling in human BM-MSCs, thereby preventing them from differentiating into CAFs induced by the TME and the ensuing effects on preneoplastic lesions (69).

Active ingredients from natural products can also target CAFs by modulating the TGF- β signaling pathway. For example, artemisinin and its derivatives have been found to inhibit TGF- β signaling, thereby inactivating cancer-associated fibroblasts and inhibiting cancer metastasis (70). Additionally, tetrahydrocannabinol and cannabidiol, either alone or in combination, inhibit TGF- β -induced interactions between CAFs and cancer cells (71). Furthermore, chestnut extract combined with TGF- β 1 has shown synergistic effects on the presence of polymerized α -SMA stress fibers, particularly in CAFs (72).

In CRC, the natural herbal compounds curcumin and chelerythrine chloride have been found to modulate the TGF- β 2/Smad2/3 axis, effectively inhibiting cancer cell invasion and migration by intervening in CAF activity (73,74). In breast cancer, curcumin effectively inhibited the CAF phenotype by a mechanism associated with a significant reduction in prostaglandin E2 and TGF- β production (75).

Silibinin, a flavonoid isolated from the fruit of the chrysanthemum plant *Silybum marianum*, has recently been shown to target CAF-mediated prostate cancer aggressiveness by inhibiting the expression of the TGF- β 2-related pathway (76,77).

Despite the considerable therapeutic potential of these natural compounds, their low bioavailability remains a significant limitation. Consequently, the development of nanomedicines to enhance bioavailability has garnered increasing attention. Furthermore, fibroblasts within the TME undergo phenotypic and functional changes, typically driven by interactions with tumor cells; these transformed cells are known as CAFs. Therefore, inhibiting the activation of CAFs can effectively regulate tumor progression at its early stages. For example, mPEG-poly(lactic-co-glycolic acid) (PLGA) nanoparticles loaded with baicalein have been developed, showing high drug

loading capacity, stability, biocompatibility and low toxicity. In breast cancer models, this formulation inhibits TGF- β /Smad and TGF- β /MAPK signaling pathways, reduces CAF activation and ultimately enhances chemotherapy efficacy (78).

In pancreatic cancer treatment, a two-stage combined therapy has been introduced, comprising the TGF- β receptor I inhibitor SB525334 and docetaxel micelles. This approach decreases TGF- β secretion and suppresses the activity of myofibroblastic (my)CAF, identified by α -SMA and FAP α expression, thereby improving therapeutic outcomes (79).

Overall, research on modulating CAFs via inhibition of the TGF- β signaling pathway has not only focused on suppressing the pro-tumorigenic functions and activity of CAFs but also on disrupting tumor-stroma interactions, as exemplified by agents such as Met and pirfenidone. Within the TME, fibroblasts undergo phenotypic and functional transitions typically driven by interactions with tumor cells, resulting in the emergence of CAFs. Notably, targeting the TGF- β pathway can reprogram CAFs, as demonstrated by curcumin, and prevent the differentiation of naïve fibroblasts into CAF phenotypes using compounds such as Nano-baicalein, LY364947 and silibinin, thereby inhibiting tumor initiation at early stages.

Although strategies targeting CAF markers such as FAP have been explored, they do not directly intervene in the key signaling pathways, such as TGF- β , that have been extensively summarized, leaving the precise characteristics of TGF- β -targeted CAF modulation insufficiently understood. Due to the specificity of stromal-targeted therapies, efficacy evaluations have predominantly relied on preclinical models.

In summary, among the various approaches targeting the TGF- β pathway, those involving small molecule natural compounds to reprogram CAF function or prevent fibroblast-to-CAF differentiation appear most mature and selective toward CAFs, offering the advantage of functional stromal remodeling rather than mere depletion. These strategies demonstrate promising prospects for clinical translation, although further studies are needed to optimize specificity and confirm efficacy in human settings.

NF- κ B signaling pathway inhibitors. The NF- κ B signaling pathway consists of receptor and receptor proximal signaling interface proteins, the inhibitor of NF- κ B (I κ B) kinase complex, I κ B protein and NF- κ B dimer. When cells are

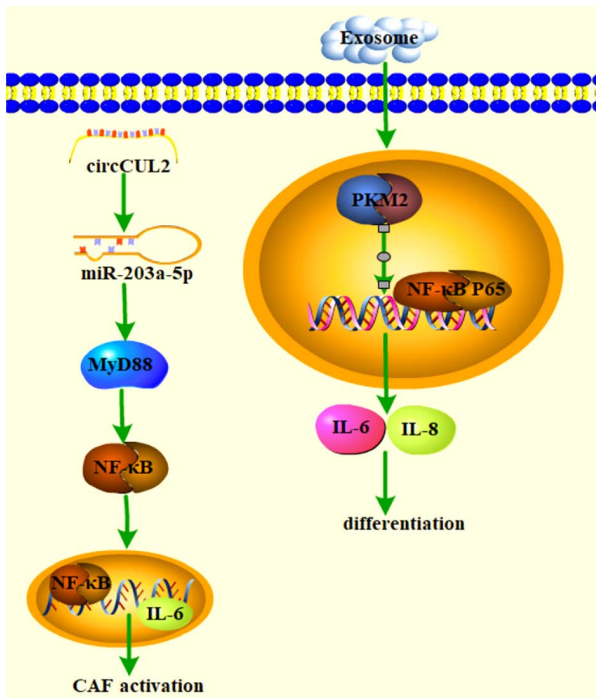


Figure 4. CircCUL2 and tumor-secreted exosomes promote CAF differentiation and activation through activation of the NF- κ B signaling pathway. CAFs, cancer-associated fibroblasts; NF- κ B, nuclear factor κ B; MyD88, myeloid differentiation primary response 88; IL, interleukin.

subjected to various intracellular and extracellular stimuli, I κ B kinase is activated, leading to the phosphorylation and ubiquitination of the I κ B protein. This process results in the degradation of the I κ B protein and the release of the NF- κ B dimer, which is further activated by various post-translational modifications (80).

The classical NF- κ B signaling pathway is closely associated with various aspects of cancer biology, including CAF progression, secretory phenotype and immunosuppressive functions. Activation of the NF- κ B signaling pathway promotes tumor growth, migration and invasion. Evidence suggests that NF- κ B signaling activation facilitates CAF activation (Fig. 4). For instance, circular RNA circCUL2 (hsa_circ_0000234) is specifically expressed in CAFs and in pancreatic ductal adenocarcinoma; circCUL2 induces an inflammatory CAF phenotype through the activation of the MYD88 innate immune signal transduction adaptor (MyD88)-dependent NF- κ B signaling pathway, establishing a distinct fibroblast ecological niche for cancer progression (81).

Exosomes from gastric cancer have been found to promote the differentiation of MSCs into CAFs by acetylating the NF- κ B P65 signaling pathway, thereby inducing aberrant metabolic and inflammatory activation (82). CD146, a cell membrane protein, has been associated with various human cancers. A study found that CD146 knockdown promoted CAF activation by potentially inducing the production of pro-tumorigenic factors through the regulation of NF- κ B activity (83). Eukaryotic translation initiation factor 4A3 (EIF4A3), a core component of the exon junction complex, has a crucial role in pre-mRNA splicing. Evidence suggests that EIF4A3 stabilizes the expression of long non-coding

RNA AGAP2-AS1, activates CAFs through MyD88/NF- κ B signaling and thus exacerbates lung cancer, revealing a new regulatory axis in lung cancer (84).

In summary, activation of the NF- κ B signaling pathway facilitates the activation or transformation of CAFs and subsequently promotes tumor progression. Conversely, inhibition of the NF- κ B pathway can eliminate CAFs and increase drug sensitivity. Genes in the NF- κ B signaling pathway may represent potential cancer therapeutic targets (Table IV) (85-93).

NF- κ B inhibitors can be used alone or in combination with chemotherapeutic agents to treat cancer and prevent recurrence. For example, chloroquine (CQ) and hydroxychloroquine (HCQ) are known antimalarials that have been successful in treating autoimmune and oncologic diseases. CQ and HCQ normalize the tumor-associated vascular system and stimulate cancer-associated fibroblasts through mechanisms related to the regulation of the Toll-like receptor 9 (TLR9)/NF- κ B pathway (85). Melatonin has been reported to indirectly reduce the proliferation and invasion of gastric cancer cells by affecting cancer-associated fibroblasts, with the mechanism involving the regulation of the NF- κ B pathway (86). Although REPERTAXIN is an IL-8 receptor (CXCR1/2) inhibitor, it effectively attenuates the protection of CAFs against CD8⁺ T cytotoxicity-resistant cancer cells by a mechanism that may be related to reduced levels of phosphorylated (p)-P38, p-JNK and p-NF- κ B (87). In addition, bepotastine, an approved H1 antihistamine, inhibited the senescence-associated secretory phenotype (SASP) of CAFs induced by poly (ADP-ribose) polymerase inhibitors (PARPi) at clinical serum concentrations. It was further demonstrated that bepotastine attenuated PARPi resistance in fibroblast-promoted tumors in three-dimensional organotypic cultures and homologous recombination-deficient patient-derived xenograft models. Mechanistically, bepotastine inhibits PARPi-triggered SASP by inhibiting NF- κ B signaling independent of histamine H1 receptors (88).

Additionally, Jianpi Jiedu Recipe (JPJDR), a classic traditional Chinese medicine prescription, can prevent CRC liver metastasis by blocking CAF activation through the regulation of the integrin β -like 1 (ITGBL1)-TNF- α -induced protein 3 (TNFAIP3)-NF- κ B signaling pathway, providing experimental evidence for its clinical application in preventing and treating CRC metastasis (89). Furthermore, the aforementioned polysaccharide MPSSS extracted from shiitake mushrooms can alter the function of prostate CAFs by activating the TLR4-NF- κ B pathway, providing a new strategy for comprehensive tumor treatment (90). Similarly, ligustilide can modulate the immunosuppressive function of CAFs by affecting the TLR4-NF- κ B pathway, thereby restoring T-cell proliferation previously inhibited by CAF supernatant (91).

CAF s have been suggested to be an important factor in inducing early metastasis and postoperative recurrence tendency in triple-negative breast cancer (TNBC) due to its characteristics of inducing dysfunction and promoting tumor metastasis. Chen *et al* (92) found that Bruceine D, an active compound derived from the Chinese herb *Brucea javanica*, inhibited CAFs-promoted TNBC metastasis by suppressing Notch1-Jagged1/NF- κ B (p65) signaling. In addition, the herb is commonly used in clinical practice against *Scutellaria barbata* D. Don and *Scleromitrium diffusum* (Willd.) R.J. Wang for its anti-tumor properties. Using a combination of bioinformatics

Table IV. Small-molecule compounds inhibiting CAF-induced cancer through suppressing NF-κB signaling pathways.

First author/s, year	Name	Target	Type of cancer	Study type	Anticancer mechanisms	(Refs.)
De Sanctis, 2023	Chloroquine and hydroxychloroquine	NF-κB	Lung cancer	Preclinical	Improved tumor microenvironment	(85)
Liu, 2021	Melatonin	NF-κB	Gastric cancer	Preclinical	Improved CAF-induced tumor microenvironment	(86)
Lou, 2024	Repertaxin	NF-κB	Gastric cancer	Preclinical	Improved CAF-induced tumor microenvironment	(87)
Jin, 2023	Bepotastine	NF-κB	Ovarian cancer	Preclinical	Improved CAF-induced tumor microenvironment	(88)
Li, 2022	Jianpi Jiedu Recipe	NF-κB	Colorectal cancer	Preclinical	Blocked CAF activation	(89)
Xu, 2019	<i>Lentinus edodes</i> polysaccharides	NF-κB	Prostate cancer	Preclinical	Impaired immunosuppressive function of CAFs	(90)
Ma, 2019	Ligustilide	NF-κB	Others	Preclinical	Blocked CAF activation	(91)
Chen, 2024	Bruceine D	NF-κB	TNBC	Preclinical	Inhibited CAF-promoted TNBC transfer	(92)
Pan, 2024	<i>Scutellaria barbata</i> D. Don and <i>Scleromitron diffusum</i> (Willd.) R.J.Wang	NF-κB	TNBC	Preclinical	Blocked CAF activation	(93)

CAFs, cancer-associated fibroblasts; NF-κB, nuclear factor κB; TNBC, triple negative breast cancer.

and *in vitro* and *in vivo* experiments, researchers have found that the herb inhibits the progression of TNBC through inhibition of NF-κB activation triggered by CAFs-derived IL-6 in *S. barbata* and *S. diffusum* (93).

Overall, research exploring the regulation of CAFs through inhibition of the NF-κB signaling pathway has extended beyond merely suppressing the pro-tumorigenic activities and activation of CAFs, as seen with agents such as JPJDR and Ligustilide, to also enhancing chemosensitivity with compounds such as Bepotastine. Additionally, CAF-induced immunosuppression remains a major barrier to effective cancer therapy and studies have demonstrated that targeting the NF-κB pathway with drugs such as MPSSS and Repertaxin can effectively mitigate immune resistance, thus opening new avenues to potentiate immunotherapeutic outcomes. Although therapies directed at CAF surface markers have been explored, they frequently bypass critical intracellular signaling cascades, including NF-κB, that govern CAF behavior, leaving the precise characteristics of NF-κB-targeted CAF interventions insufficiently defined. Furthermore, due to the complexity and context-dependent nature of stromal-targeted treatments, current evaluations of therapeutic efficacy primarily rely on preclinical models.

In summary, the most advanced and selective approaches targeting the NF-κB pathway in CAFs combine inhibition of CAF activation with the reversal of immunosuppressive functions, favoring stromal reprogramming over outright depletion. These strategies hold substantial promise for clinical translation, contingent upon further refinement

to ensure specificity and durable therapeutic effects in patients.

FAP signaling inhibitors. FAP, a membrane-bound glycoprotein, is upregulated in CAFs but not in normal fibroblasts (94). FAP is positive in >90% of human cancers, making it a promising universal target for solid tumors (95). A phase I clinical study found that sibtrotuzumab can inhibit tumor progression by specifically targeting and inhibiting CAFs in patients with FAP-positive cancers (96). Another clinical trial with iodine 131-labeled monoclonal antibody F19 (131I-mAbF19) demonstrated inhibition of tumor metastasis by recognizing FAP-specific depletion of CAFs (97).

Activated CAFs and their secreted collagen contribute to a dense fibrotic stroma that impedes drug penetration and characterizes pancreatic ductal adenocarcinoma (PDAC) as an immune-desert tumor. In a clinical study on PDAC, combination treatment with paricalcitol and hydroxychloroquine alongside gemcitabine reduced the number of fibroblasts expressing Ki67, FAP and SMA, while concurrently decreasing autophagy-related transcripts (98), indicating that this regimen enhances chemosensitivity and improves therapeutic outcomes in PDAC. Similarly, preclinical studies have demonstrated that *in vivo* administration of FAP-targeted chimeric antigen receptor macrophages (FAP-CAR-M), engineered to eliminate activated CAFs marked by FAP, markedly reduced markers of activated CAFs (FAP), collagen volume fraction and Coll1a1 secretion in murine models. These findings suggest that FAP-CAR-M represent a potential therapeutic strategy to

overcome the fibrotic barrier and thereby potentiate chemotherapy and immunotherapy against PDAC (99).

Additionally, in mouse models of epithelial-derived solid tumors, preclinical studies have found that PT630 can target FAP to reduce the content of CAFs and blood vessel density in tumors, thereby inhibiting stromatogenesis, angiogenesis and ECM remodeling, ultimately suppressing tumor growth (100). AMD3100, a CXCL12 receptor chemokine (C-X-C motif) receptor 4 inhibitor removes FAP-expressing CAFs to immunosuppress tumor growth in PDA-bearing mice, revealing the anti-tumor effects of immunotherapeutic antibodies (101). Natural active ingredients have great potential in targeting FAP and thus inhibiting CAFs.

Oxidized omphalidine (Om) is an alkaloid compound and one of the active components of bitter ginseng in Chinese medicine. Om effectively inhibits the activation of CAFs and promotes T-cell infiltration across CAFs by downregulating the expression of FAP and α -SMA (102). This intervention may lead to promising therapeutic directions for the treatment of TNBC.

Trigonelline (TGN), an alkaloid found in medicinal plants such as *Coffea spp.* and *Trigonella foenum-graecum* (fenugreek), has exhibited notable anticancer properties across various malignancies. A recent study revealed that TGN reduces fibroblast-to-CAF conversion by downregulating α -SMA and FAP expression in bladder cancer, indicating its ability to normalize the TME. These results suggest that TGN has potential to alleviate chemoresistance and thereby enhance chemotherapeutic efficacy (103).

Similarly, rosmarinic acid (RA) treatment markedly attenuated CAF activation markers and reversed EMT-related alterations in cancer cells, resulting in reduced tumor growth in CAF-enriched xenograft models. The combination of RA with gefitinib exhibited enhanced antitumor effects compared with gefitinib monotherapy (104). Echinocandin A (Ech A), a marine substance isolated from sea urchins, is a strong antioxidant. A study has reported that Ech A attenuates CAFs-induced lung cancer cell migration, which is accompanied by a decrease in the expression levels of CAF markers, waveform proteins and FAP (105).

In addition, nanomaterial-based drug delivery systems are particularly promising for cancer therapy. Leveraging the self-assembly properties of amphiphilic peptides, researchers developed a smart transformer-like drug delivery system based on cleavable amphiphilic peptides that specifically respond to FAP- α expressed on CAFs in the TME, achieving enhanced drug delivery and promising antitumor effects (106). In addition, a CAF-associated ITGB1-inactivating peptide-rich membrane nanodelivery system (designated PMNP-D) has been shown to target both CAFs and tumor cells to enhance chemotherapy by promoting drug infusion. After prolonged blood circulation and active targeting of the tumor site, PMNP-D triggers the release of FNIII14 in response to CAFs overexpressing FAP- α , which binds to ITGB1 and inhibits the biological function of CAFs to produce stromal matrix, thereby loosening the condensed stromal structure and enhancing the permeability of nanotherapeutic agents in the tumor (107). In breast cancer treatment, a novel polymeric nanoparticle system targeting CAFs has been developed by encapsulating synthetic 8-O-methylfusarubin (OMF) within nanoparticles

modified with anti-FAP antibodies (OMF@NPs-anti-FAP). This formulation showed markedly enhanced cytotoxicity in 3D spheroid models. Compared with low-FAP-expressing cells such as MCF-10A, HDFa and PC-B-142 CAFs, the high-FAP-expressing PC-B-132 CAF cells exhibited markedly higher levels of cell death, as confirmed by flow cytometry. These findings suggest that the developed high-specificity OMF-loaded polymeric nanoparticle system may serve as a promising nanopatform for improved breast cancer therapy (108). Similarly, in breast cancer, a biomimetic nanodrug system (FAP-C NPs) was engineered by fusing 4T1 cell-derived extracellular vesicles with FAP single-chain antibody fragments to form a biomimetic shell around calcipotriol-loaded PLGA nanoparticles. Experimental evidence demonstrated that FAP-C NPs could revert activated CAFs to a quiescent state, thereby neutralizing their pro-tumor functions, inhibiting cancer cell stemness, promoting dendritic cell maturation and alleviating the immunosuppressive effects of CAFs on lymphocytes. Furthermore, when combined with radiotherapy, this biomimetic nanosystem inhibited CAF activation, enhanced radiosensitivity and elicited a robust anti-tumor immune response, evidenced by a twofold increase in cytotoxic T-cell infiltration in the TME, ultimately suppressing tumor growth effectively. These results highlight the great potential of FAP-C NPs as a targeted therapeutic strategy in breast cancer treatment (109).

Meanwhile, phototherapeutic techniques have been used to target CAFs in tumors. Investigators developed a novel near-infrared photoimmunotherapy technique focusing on FAP, which specifically induced rapid cell death *in vitro* and *in vivo* mouse xenograft models with no adverse effects (110). Notably, the combination of photodynamic therapy and nanoparticles could substantially improve the ability to eradicate CAFs and induce broad-spectrum anticancer effects. Researchers used ferritin, a compact protein cage of nanoparticles, as a photosensitizing carrier and coupled FAP-specific single-chain variable fragments to the surface of ferritin to create a nanoparticle-based photoimmunotherapy (nano-PIT). This method effectively eliminated CAFs from tumors by light irradiation enabled by nano-PIT while causing minimal damage to healthy tissues due to the localized nature of the treatment (111).

Other researchers developed a photodynamic therapy method called α FAP-Z@FRT, which is based on ZnF16Pc (a photosensitizer) loading and FAP-specific single-chain variable-fragment conjugated apoferritin nanoparticles. This method is also effective in eradicating CAFs from tumors without causing systemic toxicity (112). The aforementioned results imply that the FAP-targeting polymersomes-based delivery system has the potential to be an excellent tool for cancer therapy.

FAP represents the most extensively studied and clinically advanced target among the various strategies aimed at modulating CAFs. Therapeutic agents targeting FAP not only inhibit CAF activation, thereby attenuating tumor progression and the fibroblast-to-CAF transition, as exemplified by compounds such as RA and Echinocandin A, but also serve as direct targets for drug delivery systems that selectively suppress CAFs. Noteworthy examples include transformable peptide nanocarriers, FNIII14 peptide-enriched membrane nanocarriers and polymeric nanoparticles loaded with 8-O-methylfusarubin, all

Table V. Small-molecule compounds inhibiting CAF-induced cancer through suppressing FAP signaling.

First author/s, year	Name	Target	Type of cancer	Study type	Anticancer mechanisms	(Refs.)
Scott, 2003	Sibrotuzumab	FAP	NSCLC	Phase I	Depleted CAFs to suppress tumor progression	(96)
Welt, 1994	Iodine 131-labeled monoclonal antibody F19	FAP	Colorectal carcinomas	Phase I	Inhibited the function of CAFs to suppress cancer progression	(97)
Nagaraju, 2025	Paricalcitol and hydroxychloroquine alongside gemcitabine	FAP	Pancreatic ductal adenocarcinoma	Phase I	Decreases the number of Ki67, FAP and α -smooth muscle actin-expressing CAFs	(98)
Wang, 2025	FAP-targeted chimeric antigen receptor macrophages	FAP	Pancreatic cancer	Preclinical	Reduced markers of activated CAFs	(99)
Santos, 2009	PT630	FAP	Lung cancer	Preclinical	Reduced CAF levels in the tumor	(100)
Feig, 2013	α FAP-PE38	FAP	Breast cancer	Preclinical	Inhibited the function of CAFs to suppress cancer progression	(101)
Wang, 2023	Oxymatrine	FAP	Triple negative breast cancer	Preclinical	Blocked CAF activation	(102)
Kao, 2025	Trigonelline	FAP	Bladder cancer	Preclinical	Reduced CAF levels in the tumor	(103)
Li , 2025	Rosmarinic acid	FAP	NSCLC	Preclinical	Attenuated CAF activation	(104)
Eum, 2024	Echinochrome A	FAP	Lung cancer	Preclinical	Inhibited CAF-induced mediated lung cancer cell migration	(105)
Ji, 2016	Drug-loadedCAP-NPs	FAP	Prostate cancer	Preclinical	Disrupted the matrix barrier of the drug	(106)
Liu, 2023	FNIII14 peptide-enriched membrane nanocarrier	FAP	Adenoid cystic carcinoma	Preclinical	Inhibited CAF produced substrate	(107)
Rodponthukwaji, 2024	OMF@NPs-anti-FAP	FAP	Breast cancer	Preclinical	Promoted CAF-induced apoptosis	(108)
Gao, 2025	FAP-C NPs	FAP	Breast cancer	Preclinical	Inhibited the activation of CAFs	(109)
Zhou, 2021	α FAP-Z@FRT	FAP	Lung cancer	Preclinical	Stimulated immunization against CAF	(112)

CAFs, cancer-associated fibroblasts; FAP, fibroblast activation protein; NSCLC, non-small cell lung cancer; NPs, nanoparticles.

of which have demonstrated promising efficacy across diverse cancer models. Among the distinct molecular pathways implicated in CAF regulation, approaches centered on FAP inhibition stand out for their maturity, specificity and capacity to reprogram the tumor stroma rather than solely deplete fibroblast populations. Consequently, FAP-targeted interventions exhibit superior selectivity towards CAF populations and hold significant translational potential, underscoring their leading

role in the clinical advancement of matrix-focused cancer therapies (Table V) (96-109,112).

3. Other signaling pathways or target regulators

Beyond the aforementioned pathways, additional axes, including TLR4, hypoxia-inducible factor 1 α (HIF-1 α), Wnt, G protein-coupled estrogen receptor (GPER) and PDGFR, also

Table VI. Small-molecule compounds inhibiting CAF induced cancer through suppressing various signaling pathways.

First author/s, year	Name	Target	Type of cancer	Study type	Anticancer mechanisms	(Refs.)
Mei, 2020	Cinnamaldehyde	TLR4	Prostate cancer	Preclinical	Inhibited the inhibitory effect of CAF T cells	(113)
Wang, 2021	Polysaccharides from <i>Lentinus edodes</i>	TLR4	Colorectal cancer	Preclinical	Decreased CAF secretion VEGF-C	(114)
Ma, 2022	Ligustilide	TLR4	Prostate cancer	Preclinical	Downregulated VEGFA secretion in prostate CAF	(115)
Lappano, 2015	Calixpyrroles	GPER	Breast cancer	Preclinical	Inhibited the proliferation of CAF	(117)
Maggiolini, 2015	Benzo(b)pyrrolo (1,2-d)(1,4)oxazin-4-one structure	GPER	Breast cancer	Preclinical	Inhibited the stimulatory effect of CAF	(118)
Shao, 2020	Metformin	HIF-1 α	Breast cancer	Preclinical	Prevented tumor-stromal crosstalk in breast cancer	(62)
Du, 2015	Curcumin	HIF-1 α	Prostate cancer	Preclinical	Suppressed CAF-driven prostate cancer invasion	(120)
Kinoshita, 2010	Imatinib	PDGF	Lung cancer	Preclinical	Inhibited CAF proliferation	(122)
Pietras, 2008	Imatinib	PDGF	Cervical carcinoma	Preclinical	Inhibited the matrix-supportive function of CAFs	(123)

CAFs, cancer-associated fibroblasts; TLR4, Toll-like receptors 4; VEGF, vascular endothelial growth factor; GPER, G-protein-coupled estrogen receptor; HIF-1 α , hypoxia inducible factor 1 α ; PDGF, platelet-derived growth factor.

shape the bidirectional crosstalk between CAFs and cancer cells, with context-specific features that create complementary intervention points (Table VI) (62,113-123). Collectively, these pathways regulate immune suppression, (lymph)angiogenesis, metabolic reprogramming and hormone signaling, thereby influencing tumor progression.

TLR4-centered signaling exemplifies the immune- and angiogenesis-related dimensions of CAFs function. Cinnamaldehyde alleviates CAFs-mediated T-cell suppression in a TLR4-dependent manner, functionally reprogramming CAFs and offering therapeutic potential (113). In CRC, the polysaccharide MPSSS reduces lymphangiogenesis by decreasing CAFs-derived VEGF-C via the TLR4/JNK pathway, suggesting a strategy for comprehensive treatment (114). Similarly, ligustilide downregulates VEGFA levels in CAFs through a TLR4-related pathway, thereby blocking CAFs-driven angiogenesis and highlighting the anti-angiogenic promise of natural active molecules (115).

GPR30 (also known as GPER), a member of the G protein-coupled receptor family, mediates estrogen signaling in various types of normal and malignant cells, leading to specific gene markers, as well as the migration and proliferation of cancer cells and CAFs (116). Investigators synthesized cuprolyl derivatives to act as GPER antagonists, which effectively inhibited CAFs from stimulating cancer progression in the TME (117). Additionally, two novel selective GPER

antagonists based on the structure of benzo(b)pyrrolo(1,2-d)(1,4)oxazin-4-one were synthesized to inhibit the stimulatory effect of CAFs on cancer progression in breast cancer (118).

HIF-1 α is closely related to CAFs migration and invasion. In a nude mouse subcutaneous xenograft model, upregulation of HIF-1 α expression promotes CAF migration and invasion via miR-210, which leads to CRC metastasis and increases patient mortality (119). Therefore, inhibition of HIF-1 α expression is beneficial in inhibiting CAF migration and invasion, thus suppressing cancer progression. HIF-1 α signaling in CAFs promotes tumor progression mainly by regulating glycolytic metabolism. Met, a diabetes drug, was found to inhibit HIF-1 α signaling in CAFs, leading to reduced breast cancer cell invasion (62). Furthermore, curcumin, an active ingredient of Chinese medicine, eliminated CAF-induced invasion and EMT through a mechanism related to its inhibition of monoamine oxidase A/mTOR/HIF-1 α signaling in prostate cancer (120).

PDGF, a disulfide-linked dimer, is a potent mitogen in various cancer cell types, including glioma, sarcoma, pancreatic and prostate cancers. A study has shown that PDGF-associated receptors are expressed by cancer-associated stromal cells, pericytes and CAFs in human colon cancer (121). Imatinib, a small-molecule tyrosine kinase inhibitor, has shown promising antitumor activity. Mechanistic studies revealed that its antitumor activity is mediated by blocking PDGF signaling,

thereby reducing the proliferation-stimulating effect of CAFs on lung cancer cells (122). Similarly, in a mouse model of human cervical cancer, imatinib inhibited the stromal PDGF receptor, leading to reduced proliferation and angiogenesis of cervical lesions by inhibiting CAFs-expressed angiogenic factors, such as fibroblast growth factor 2 (FGF-2) and epithelial cell growth factor FGF-7 (123).

4. Selective inducers of cell death

Cell death encompasses multiple, mechanistically distinct modalities, including apoptosis, necroptosis, ferroptosis, pyroptosis and necrosis, each defined by characteristic morphological and biochemical signatures, while autophagy represents a stress-adaptive catabolic process that can intersect with and, in certain contexts, contribute to cell death. During tumor evolution and therapy, cancer cells can undergo diverse forms of regulated cell death, notably apoptosis, autophagy-associated cell death and ferroptosis. Beyond classical apoptosis-inducing agents traditionally used to eliminate tumor cells and, in certain strategies, CAFs, emerging approaches that suppress CAFs by triggering autophagy or ferroptosis have shown preclinical efficacy in curbing recurrence and metastasis. Representative interventions, targets and outcomes are summarized in Table VII (65,129-149), underscoring the therapeutic potential of modulating multiple death pathways within the TME.

Ferroptosis and CAFs. Ferroptosis is a recently characterized, iron-dependent form of programmed cell death that is mechanistically distinct from apoptosis, necrosis and autophagy. It is driven by divalent iron and ester oxygenases that catalyze peroxidation of polyunsaturated fatty acids within membrane phospholipids, leading to lethal lipid-reactive oxygen species (ROS) accumulation. This lipid peroxidation is normally counteracted by the glutathione system, with glutathione peroxidase 4 (GPX4) as the core enzyme; decreases in GPX4 activity and glutathione availability sensitize cells to ferroptosis (124). Within the TME, CAFs modulate therapy response in part by suppressing ferroptosis, thereby fostering drug resistance. CAFs-secreted exosomal miR-522, for example, targets arachidonate 15-lipoxygenase to block lipid-ROS accumulation and inhibit ferroptosis in cancer cells, ultimately reducing chemotherapy sensitivity (125). Similarly, CAFs-derived exosomal miRNAs that target acyl-CoA synthetase long chain family member 4 (ACSL4) inhibit ferroptosis and induce gemcitabine resistance in pancreatic cancer cells (126). Beyond exosomal signaling, CAFs can reprogram cysteine metabolism to boost glutathione synthesis and increase resistance to ferroptosis in pancreatic cancer (127). These findings collectively support ferroptosis as a promising axis for CAFs-focused intervention. Although research on ferroptosis activators is broad, relatively few small molecules have been designed to target CAFs by mediating ferroptosis; accordingly, this article summarizes small-molecule approaches to modulate ferroptosis in the context of CAFs (Fig. 5).

Importantly, CAF-derived signals are context dependent and can also sensitize tumors to ferroptosis. CAFs exosomal disheveled binding antagonist of beta catenin 3 antisense 1 (DACT3-AS1) acts as an inhibitory regulator

of malignant transformation and oxaliplatin resistance by inducing ferroptosis, characterized by decreased GPX4 and solute carrier family 7 member 11 (SLC7A11) expression, reduced GSH levels and suppression of oxaliplatin-treated cells; the ferroptosis inhibitor ferrostatin-1 reverses these effects, indicating that DACT3-AS1 engages ferroptotic mechanisms in oxaliplatin-treated gastric cancer cells (128). In OSCC, a podoplanin-positive CAFs subset promotes invasiveness by inhibiting ferroptosis in tumor cells via the FTX/flap structure-specific endonuclease 1 (FEN1)/ACSL4 signaling cascade; treatment with the ferroptosis activator RSL-3 suppresses the tumorigenic potential of OSCC cells overexpressing FEN1 *in vitro* and *in vivo* (129). Leveraging the prevalence of FAP overexpression in >90% of human tumors, exocrine-like nanovesicles (eNVs-FAP) derived from FAP-engineered tumor cells have been developed as a tumor vaccine that promotes tumor ferroptosis and inhibits growth by releasing interferon- γ (IFN- γ) from cytotoxic T lymphocytes while depleting FAP+ CAFs (130). Ferroptosis also intersects with antitumor immunity: In gastric cancer, CAFs as a major immunosuppressive component can induce ferroptosis in natural killer (NK) cells through iron regulation, impairing their cytotoxic function and promoting tumor progression and immune escape. In patient-derived organoid models, functional targeting of CAFs using the iron chelator deferoxamine combined with a follistatin like protein 1-neutralizing antibody alleviates CAFs-induced ferroptosis in NK cells and enhances their cytotoxicity against gastric cancer (131). Similarly, CAFs-induced resistance to immunotherapy is closely linked to anoctamin 1 (ANO1)-mediated inhibition of cancer cell ferroptosis; ANO1 upregulates nuclear factor erythroid 2-related factor 2/SLC7A11 via a PI3K-Akt-dependent pathway, whereas the ferroptosis agonist erastin reverses ANO1-driven suppression of lipid ROS and malondialdehyde and mitigates ANO1's malignant effects (132).

Together, these studies delineate a bidirectional relationship between CAFs and ferroptosis: CAFs can impede ferroptosis to support drug resistance and immune evasion, yet they can also be targeted or leveraged to restore ferroptotic vulnerability and resensitize tumors. Practically, integrating ferroptosis modulators, whether small molecules such as RSL-3 and erastin or targeted nanovesicle platforms such as eNVs-FAP, into CAF-centric strategies offers a route to counteract stromal protection, enhance chemotherapy efficacy and strengthen antitumor immunity.

Apoptosis and CAFs. Apoptosis is a genetically programmed, autonomous and orderly form of cell death that preserves tissue homeostasis by removing damaged or superfluous cells, thereby enabling improved adaptation to the micro-environment. Within the TME, CAFs are pivotal drivers of tumorigenesis, progression and migration; accordingly, eliminating CAFs or attenuating their tumor-promoting activity can facilitate tumor immunotherapy (133). It has been reported that CAFs exhibit tumor-promoting properties by inhibiting apoptosis of tumor cells; however, evidence also suggests that CAFs may stimulate apoptosis of tumor cells (134). These observations position apoptosis as a tractable regulatory node for modulating CAF activity. Although the available evidence suggests that CAF apoptosis may be a double-edged sword,

Table VII. Small-molecule compounds inhibiting CAF-induced cancer through regulating ferroptosis, apoptosis and autophagy.

First author/s, year	Name	Target	Type of cancer	Study type	Anticancer mechanisms	(Refs.)
Li, 2023	FER-1	Ferroptosis	Gastric cancer	Preclinical	Inhibited CAF-derived DACT3-AS1	(129)
Li, 2023	RSL-3	Ferroptosis	Oral squamous cell carcinoma	Preclinical	Inhibited CAFs with podoplanin positive expression	(129)
Hu, 2021	eNVs-FAP	Ferroptosis	Colon, melanoma, lung and breast cancer	Preclinical	Inactivated CAFs	(130)
Yao, 2023	Combination of deferoxamine and FSTL1 neutralizing antibody	Ferroptosis	Gastric cancer	Preclinical	Inactivated CAFs	(131)
Li, 2020	Disulfiram/copper	Apoptosis/	Inactivated CAFs	Preclinical		(135)
ferroptosis	Nasopharyngeal cancer	Preclinical				
Lee, 2018	Bortezomib and panobinostat	Apoptosis	Breast cancer	Preclinical	Reduced the viability of CAFs	(136)
Mediavilla-Varela, 2016	Pirfenidone	Apoptosis	Lung cancer	Preclinical	Induced lung CAF apoptosis	(65)
Zeng, 2020	Curcumin	Apoptosis	Others	Preclinical	Promotion of CAF apoptosis by ROS-mediated endoplasmic reticulum stress	(137)
Han, 2020	Cinnamaldehyde	Apoptosis	Prostate cancer	Preclinical	Inhibited CAF proliferation and promoted CAF apoptosis	(138)
Chang, 2018	Nab-paclitaxel	Apoptosis	Cholangiocarcinoma	Preclinical	Destroyed CAF	(139)
Donthireddy, 2022	ONP-302 nanoparticles	Apoptosis	Others	Preclinical	Induced CAF apoptosis	(140)
Chen, 2016	Nanoliposome with navitoclax	Apoptosis	Liver cancer	Preclinical	Specifically eradicated CAF	(141)
Shen, 2023	Nanoemulsions (DOX and siRNA)	Apoptosis	Others	Preclinical	Inhibited CAF proliferation and promoted CAF apoptosis	(142)
Zhao, 2019	Chloroquine	Autophagy	Liver cancer	Preclinical	Attenuated the stemness enhanced by CAF	(146)
Martinez-Outschoorn, 2010	Chloroquine	Autophagy	Breast cancer	Preclinical	Reduced CAF generation	(147)
Han, 2016	Polysaccharides from Polygonatum	Autophagy	Prostate cancer	Preclinical	Inhibited CAF proliferation	(148)
Ferraresi, 2017	Resveratrol	Autophagy	Lung cancer	Preclinical	Offset CAF maturity	(149)

CAFs, cancer-associated fibroblasts; ROS, reactive oxygen species.

wherein excessive depletion could perturb stromal integrity or provoke maladaptive remodeling, most current strategies intentionally promote CAF apoptosis to restrain tumor progression.

Pharmacologic and repurposed agents illustrate this approach. Disulfiram/copper (DSF/Cu), noted for clinical promise based on its anticancer activity and safety, induces

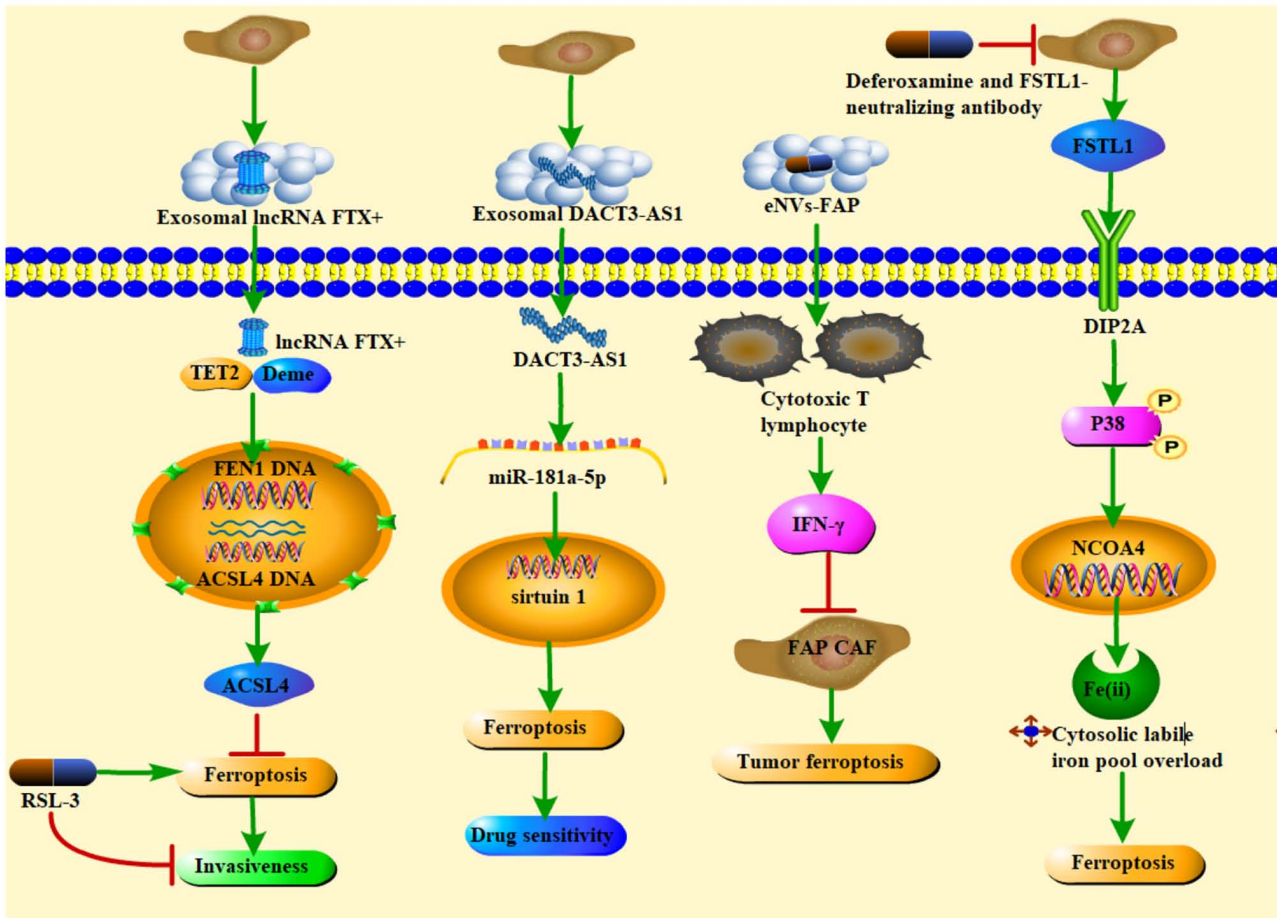


Figure 5. Small molecule compounds mediate mutual crosstalk between CAFs and ferroptosis to inhibit tumor progression or enhance chemotherapeutic drug sensitivity. RSL-3 inhibits the tumorigenesis potential of oral squamous cell carcinoma cells overexpressing FEN1; exosome DACT3-AS1 confers cancer cell sensitivity to oxaliplatin through miR-181a-5p/sirtuin 1-mediated iron death; cellular immune responses activated by the NVs-FAP vaccine can promote tumour ferroptosis by releasing IFN- γ from the CD8+ T lymphocytes (CTLs) and depleting FAP CAFs; functional targeting of CAFs with a combination of deferoxamine and FSTL1-neutralising antibody markedly alleviated CAFs-induced iron death in NK cells and enhanced NK cell cytotoxicity against GC. CAFs, cancer-associated fibroblasts; miR, microRNA; NVs, nanovesicles; FAP, fibroblast activation protein; IFN- γ , interferon- γ ; CTLs, CD8+ T lymphocytes; TET2, ten-eleven translocation 2; Deme, Demeter; FEN1, flap structure-specific endonuclease 1; ACSL4, long-chain-fatty-acid-CoA ligase 4; DACT3-AS1, DACT3 antisense RNA 1; IFN, interferon; FSTL1, follistatin-like 1; DIP2A, disco interacting protein 2 homolog A; NCOA4, nuclear receptor coactivator 4.

apoptosis in nasopharyngeal fibroblasts via an aldehyde dehydrogenase-independent mechanism; *in vivo*, DSF/Cu combined with cisplatin (CDDP) is well tolerated and markedly suppresses nasopharyngeal tumor growth both in tumor cell models and in 5-8F xenografts (135). Clinically advanced agents such as bortezomib and panobinostat have likewise emerged as anti-CAF candidates: They reduce the viability of multiple patient-derived CAF populations by inducing caspase-3-mediated apoptosis, with combination therapy outperforming either monotherapy *in vitro* and in xenografts of mouse breast cancer cells with mouse CAFs (136). Pirfenidone, an antifibrotic drug approved for idiopathic pulmonary fibrosis, triggers apoptotic death in pulmonary CAFs at high concentrations and low-dose combinations with cisplatin further increase CAF death in both co-culture systems and *in vivo* settings (65). Natural compounds add complementary mechanisms: Curcumin and cinnamaldehyde, extracted from Chinese herbs, induce apoptosis and cell-cycle arrest in prostate cancer CAFs via ROS-mediated endoplasmic reticulum (ER) stress and intrinsic apoptotic pathways, respectively (137,138).

Nanotechnology has expanded the toolkit for selectively inducing apoptosis in CAFs while potentially improving therapeutic indices. Nab-paclitaxel, an effective agent against intrahepatic cholangiocarcinoma (IH-CCA), more efficiently destroys CAFs than its prototype paclitaxel in a rat model of thioacetamide-induced spontaneous desmoplastic IH-CCA (139). Biodegradable, negatively charged ONP-302 nanoparticles have been used to induce apoptosis in CAFs within the TME (140). Targeted delivery systems further enhance specificity: Navitoclax-loaded nanoliposomes modified with the FH peptide (FH-SSL-Nav), which binds tenascin C predominantly expressed by CAFs, selectively engage apoptotic pathways in CAFs (141); similarly, nucleic acid aptamer-modified PLGA nanoemulsions effectively target CAFs and induce their apoptosis (142).

Collectively, these data support apoptosis-oriented modulation of CAFs as a rational strategy to weaken stromal support for malignancy and to potentiate standard anticancer therapies. Conceptually, the convergence of repurposed small molecules and targeted nanocarriers offers a path to enhance selectivity, reduce off-target toxicity and integrate CAF apoptosis with

cytotoxic or targeted regimens. Given the context dependence of stromal biology, careful attention to dosing, scheduling and readouts of on-target activity (e.g., cleaved caspase-3 and ER-stress biomarkers in CAFs, alongside stromal remodeling endpoints) will be essential to maximize antitumor benefit while preserving necessary tissue homeostasis, without altering the fundamental rationale and evidence base aforementioned.

Autophagy and CAFs. Autophagy is a catabolic process in which cytoplasmic proteins or organelles are sequestered into double-membrane vesicles and subsequently fuse with lysosomes to form autolysosomes that degrade their contents. Emerging evidence indicates that autophagy contributes to the metabolic and signaling interplay between tumors and CAFs, with CAFs promoting tumor growth by supplying nutrients to cancer cells through autophagic activity (143). Consistent associations between autophagy and CAF progression have been reported across breast, and prostate, cancers, supporting autophagy as a tractable node for modulating CAFs-mediated tumor support (144). Conceptually, therapeutic benefit can arise from autophagy modulation in either direction, but most current efforts emphasize inhibition of autophagy within CAFs to blunt their pro-tumor functions, while in selected contexts induction of autophagy in cancer or stromal cells can also counteract CAF-driven malignant behaviors (134).

Among autophagy inhibitors, chloroquine has been shown to abrogate the stimulatory effects of CAFs on tumor growth and to suppress the pro-carcinogenic homologous TLR4/NF- κ B signaling pathway in a mouse xenograft model (145). In HCC models, chloroquine also inhibits CAFs-induced activation of autophagic flux in cancer cells, leading to light chain (LC)3-II accumulation and increased LC3 puncta, thereby preventing CAFs from enhancing stem cell-like properties in these cells (146). In parallel, matrix caveolin-1 (Cav-1) deficiency has emerged as a stromal biomarker of CAFs associated with poor outcomes in breast cancer and ductal carcinoma *in situ*; chloroquine or other autophagy/lysosomal inhibitors may act as anticancer agents by therapeutically restoring stromal Cav-1 expression in CAFs (147). Complementing these inhibitory strategies, several interventions leverage autophagy induction to disrupt CAF-related tumor support: Polygonatum polysaccharides extracted from Chinese herbs stimulate autophagy and inhibit the growth of prostate CAFs, suggesting a novel approach centered on limiting prostate CAF expansion (148); the naturally occurring polyphenol resveratrol counters IL-6-induced migration of ovarian cancer cells by inducing autophagy in migrating frontier cells, thereby attenuating invasive and metastatic behavior (149); and resveratrol together with its analogue 4,4'-dihydroxy-trans-stilbene reduces lung carcinoma tumor mass through enhanced autophagy, which blocks the phenotypic transformation of normal fibroblasts into CAFs (150).

Taken together, these findings delineate autophagy as a context-dependent lever in the tumor-stroma ecosystem: CAF-driven autophagy can fuel tumor growth, yet judicious modulation, predominantly inhibition within CAFs and in specific scenarios induction within cancer or stromal compartments, can dismantle CAF-mediated support for malignancy. This logic argues for cell type-specific, endpoint-anchored

strategies that track autophagy dynamics (such as LC3-II accumulation and puncta) alongside stromal phenotypes such as Cav-1, enabling the selection of inhibition vs. induction to achieve sustained suppression of CAF-driven tumor progression without undermining essential tissue homeostasis.

5. CAF heterogeneity and therapeutic risks: A detailed analysis

CAF exhibit pronounced heterogeneity within the TME, as demonstrated by the research employing single-cell RNA sequencing, spatial transcriptomics and surface marker profiling (151). Distinct CAF subpopulations with discrete molecular signatures and functional phenotypes have been identified across various malignancies, including breast cancer, PDAC and NSCLC. Representative CAF subsets comprise inflammatory CAFs (iCAFs), characterized by high expression of pro-inflammatory cytokines such as IL-6 and CXCL1 (138); myCAFs, which express elevated α -SMA and are enriched in ECM components; and antigen-presenting CAFs (apCAFs), expressing major histocompatibility class II molecules capable of modulating local immune responses (152).

These CAF subsets differ not only in their spatial distribution but also in the signaling pathways they engage with and their influence on tumor biology. For instance, myCAFs predominantly rely on TGF- β signaling to maintain their contractile, matrix-remodeling phenotype, thereby contributing to fibrotic stroma formation (153). Conversely, iCAFs exhibit activation of the JAK/STAT3 pathway and secrete inflammatory factors that foster an immunosuppressive milieu (154). Importantly, despite the general tumor-promoting perception of CAFs, emerging evidence indicates that certain CAF subsets may exert tumor-restraining functions in specific contexts. For example, myCAFs have been reported to form physical barriers limiting tumor cell invasion, while apCAFs may affect anti-tumor immunity through antigen presentation mechanisms (155).

Given this functional complexity, non-selective depletion of CAFs poses significant therapeutic risks. In PDAC mouse models, ablation of α -SMA+ myCAFs paradoxically accelerated tumor progression and enhanced immune evasion, indicating a protective role of this subset under certain conditions (156). Broad CAF elimination may disrupt stromal barriers, facilitating tumor dissemination or triggering maladaptive remodeling of the TME, thereby exacerbating disease. By contrast, functional reprogramming strategies, such as inhibition of TGF- β and IL-6 signaling, have demonstrated potential to convert pro-tumorigenic CAFs into a more inert or tumor-restraining phenotype, mitigating adverse effects linked to CAF clearance. This approach has thus gained increasing attention as a more nuanced therapeutic avenue (157).

Accordingly, future CAF-targeted interventions must be founded on precise subtype identification and functional stratification. Defining subtype-specific signaling pathways and markers will enable selective targeting that minimizes collateral damage and improves therapeutic efficacy. Furthermore, advances in single-cell technologies and mechanistic studies are essential to elucidate the dynamic regulation of CAF phenotypes, bridging the gap from indiscriminate ablation toward sophisticated functional modulation of tumor stroma.

6. Discussion

The present review synthesized well-characterized CAF-associated signaling pathways, including FAP, PI3K/AKT/mTOR, JAK/STAT, NF- κ B, TGF- β , ferroptosis, autophagy and apoptosis and highlighted small-molecule modulators that act on these axes with the potential to eliminate or functionally disable CAFs, thereby supporting cancer therapy. Although biologics have progressed rapidly, small molecules remain essential in clinical practice due to lower cost and simpler generic manufacturing compared with monoclonal antibodies (158) and the present study therefore summarized these agents in Tables I-VII. As most chemotherapeutics induce varying degrees of toxicity (159-161), an appropriate balance between anticancer efficacy and adverse effects is necessary when targeting CAFs; in this context, natural compounds, typically characterized by lower toxicity and multitarget capacity, offer a promising anti-CAFs strategy despite the lengthy path from discovery to clinical use (162-165). Drug repurposing of approved agents, whose pharmacology and safety are well defined, may also provide a shortcut that reduces attrition and economic burden. Notably, FDA-approved drugs with reported anti-CAFs activity include modulators of PI3K/AKT/mTOR (such as Oxaliplatin, CDDP, Capmatinib, Regorafenib and Caffeine), JAK/STAT (Tocilizumab), TGF- β (Eribulin, Aspirin, Ibuprofen, Met, Digoxin, Pirfenidone and Nintedanib), NF- κ B (Chloroquine and Hydroxychloroquine), autophagy (Chloroquine) and apoptosis (Pirfenidone, Bortezomib, Panobinostat and DSF/Cu) and several have entered clinical evaluation. In addition, numerous natural small molecules or prescription formulations show good tolerance but require further validation of efficacy and safety, such as PI3K/AKT/mTOR modulators (Biejajian pill, Tiplaxtinin, gold nanoparticles, Mycophenolic acid, Everolimus, Dihydromyricetin and MSI-N1014), JAK/STAT modulators (Bufalin, Tranilast, Curcumin, Oroxylin A, Resveratrol, Berberine, Lentinus edodes polysaccharide and β -Carotene), TGF- β modulators (HA-PTX/MATT-LTSLs HNP, LY2157299 monohydrate, LY2109761, Halofuginone, bone morphogenetic protein and activin membrane-bound inhibitor, Artemisinin derivatives, Δ 9-Tetrahydrocannabinol and Cannabidiol, *Aesculus hippocastanum* L. extract, Curcumin, Chelerythrine chloride, Silibinin, Evodiamine and Berberine), NF- κ B modulators (Melatonin, JPJDR, Lentinus edodes polysaccharides, Ligustilide), FAP modulators (PT630, AMD3100, α FAP-PE38, drug-loaded CAP-NPs and α FAP-Z@FRT), autophagy modulators (Glycyrrhizin, Polygonatum polysaccharides and Resveratrol), apoptosis modulators [Curcumin, Cinnamaldehyde, Nab-paclitaxel, ONP-302 nanoparticles, nanoliposome with navitoclax, nano-emulsions carrying doxorubicin (DOX) and small interfering RNA (siRNA)] and ferroptosis modulators (FER-1, RSL-3 and eNVs-FAP). The present study also listed CAF-targeting compounds in phase I trials, including FAP modulators such as Sibrotuzumab and 131I-mAbF19; notably, Sibrotuzumab was reported to target and block activation of FAP-positive CAFs to inhibit tumor growth. Most other agents remain at the preclinical stage yet exhibit anti-CAF activity, suggesting that dose optimization, rational combinations and structure-guided derivative development could enhance utility, while the

potential for significant side effects underscores the need for rigorous dose-finding and toxicity monitoring. Overall, current evidence indicates that CAF-targeting compounds show acceptable tolerability in mice or patients and multitarget strategies spanning several oncogenic pathways may play a meaningful role in forthcoming clinical studies. The most tractable path to translation is to deploy these agents as short, schedule-defined CAF-priming interventions that transiently soften the matrix and reduce immune exclusion and to pair them with targeted delivery platforms that concentrate activity within the stroma; this approach retains the advantages of small molecules while mitigating risks to wound healing and systemic homeostasis.

Growing mechanistic evidence supports the use of small-molecule compounds targeting FAP, PI3K/AKT/mTOR, JAK/STAT, NF- κ B, TGF- β and autophagy to suppress CAF function and several of these agents are entering clinical evaluation. Nevertheless, most studies to date have been conducted at cellular and murine levels and trials explicitly designed to assess CAF-targeting small molecules with CAF-specific clinical endpoints remain limited. Small molecules directed at FAP demonstrate notable specificity and potent inhibitory activity against CAFs, positioning FAP as a promising clinical target to enable development of anticancer therapies. As aberrantly activated CAFs engage diverse and context-dependent signaling pathways, single-agent strategies may be insufficient; rational combination regimens that concurrently target multiple pathways are likely to yield superior outcomes.

Importantly, targeting CAFs alone is generally not adequate to treat cancer, as numerous CAF-focused small molecules do not directly kill cancer cells; combining CAF-directed agents with cytotoxic chemotherapy or targeted therapies has the potential to improve efficacy during tumor development (166). Looking ahead, a coherent framework emerges from the available data and our interpretation: CAF-focused small molecules should be integrated into combination regimens with clear pharmacodynamic anchors, reductions in matrix stiffness and collagen crosslinking, improved perfusion and enhanced effector immune-cell infiltration, to demonstrate on-mechanism stromal remodeling (10); patient selection ought to reflect CAF heterogeneity by matching drugs to dominant CAF programs such as FAP-high or TGF- β -driven phenotypes (167); dosing should favor window-of-opportunity or intermittent schedules to balance efficacy with the physiological roles of targets; and sequential strategies that pair brief CAF suppression or apoptosis with subsequent normalization or reprogramming may stabilize a permissive microenvironment and reduce rebound once drug pressure is withdrawn. These directions are supported by the dual realities that CAFs are plastic and context-dependent and that their modulation exerts system-level effects on drug delivery and immune accessibility (168). The open questions, namely which CAF subsets should be eliminated vs. functionally suppressed, how to anticipate and prevent adaptive escape and how to optimally synchronize CAFs priming with chemotherapy, radiotherapy and immunotherapy, are best answered through CAF-centric trial designs that embed stromal endpoints and leverage targeted delivery to widen the therapeutic window without altering the fundamental clinical rationale aforementioned (169).

CAFs exhibit significant heterogeneity within the TME, encompassing diverse subtypes with distinct molecular and functional characteristics. Advances in single-cell sequencing and spatial transcriptomics have identified major CAF subsets, including iCAFs, myCAFs and apCAFs, which differ in spatial distribution and active signaling pathways. MyCAFs maintain ECM remodeling largely via TGF- β signaling, whereas iCAFs rely on the JAK/STAT3 pathway to secrete pro-inflammatory factors that foster an immunosuppressive milieu (170). Notably, some CAFs subsets may exert tumor-restraining effects in specific contexts, such as myCAFs forming physical barriers that limit tumor invasion (40). Given this complexity, non-selective depletion of CAFs can inadvertently accelerate tumor progression and immune evasion, underscoring potential risks of broad CAF targeting. Therefore, precise identification and functional modulation of CAFs subtypes are critical for developing safer and more effective therapeutic strategies, with reprogramming of CAF phenotypes through pathway-specific interventions emerging as a promising approach.

In summary, CAFs serve as essential regulators within the TME, playing critical roles in tumor progression, immune suppression and therapy resistance. With increasingly comprehensive insights into their functions and mechanisms, emerging CAFs-targeted therapeutics, including small molecule inhibitors, monoclonal antibodies, immune modulators and gene editing technologies, have shown promise not only in disrupting pathogenic signaling between CAFs and cancer cells but also in effectively remodeling the TME to restore immune competence (171). However, despite these encouraging advances, several challenges remain for the clinical translation of these strategies. Ensuring safety and efficacy requires extensive validation through large-scale clinical trials, given the biological heterogeneity across patient populations that may affect therapeutic responses. Furthermore, complexities in manufacturing, quality control and delivery of such agents pose significant obstacles to widespread clinical application. Future research must leverage cutting-edge technologies such as single-cell sequencing, spatial omics and high-throughput screening to comprehensively characterize the cellular states and dynamic changes of CAFs across diverse tumor contexts, delineating their precise functions and regulatory networks. Systematic elucidation of the complex crosstalk between CAFs and other cellular components such as immune cells and cancer stem cells will uncover novel synergistic therapeutic targets and enable personalized precision medicine approaches. Realistic recapitulation of the *in vivo* tumor milieu through advanced *in vitro* models and genetically engineered animal systems remains indispensable for rigorous evaluation of drug safety and efficacy. Furthermore, exploring combinational regimens of CAF-targeted agents with existing radiotherapy, chemotherapy and immunotherapy represents a crucial strategy to overcome resistance and enhance treatment outcomes. Clinical trial designs must prioritize patient stratification and biomarker integration to improve response precision and maximize clinical benefit. Overall, addressing these clinical translation challenges through the tight integration of fundamental research and clinical application will accelerate the development and translation of CAF-targeting drugs, ultimately providing cancer patients with safer, more

effective and tailored therapeutic options, thereby advancing precision oncology into a new era.

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Authors' contributions

YW contributed to the drafting of the manuscript and was a major contributor in writing. XQL designed, conceived and supervised the study and revised the manuscript. DL conducted the literature search and analysis. KDL generated the figures. DDZ generated the tables. Data authentication is not applicable. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

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Competing interests

The authors declare that they have no competing interests.

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