Cancer Biol Med 2025. doi: 10.20892/j.issn.2095-3941.2025.0288

REVIEW

OPEN ACCESS

Harnessing the power of cancer-associated fibroblasts to revolutionize pancreatic cancer treatment

Jian Shen[1], Ruopu Wu[2], Tao Yin[1], Qun Wang[1], Lei Nie[1]

[1]Department of Hepatic & Biliary & Pancreatic Surgery, Hubei Cancer Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430079, China; [2]The First Clinical Medical School, Tianjin Medical University, Tianjin 300070, China

ABSTRACT Pancreatic cancer (PC) is a highly aggressive cancer characterized by a unique tumor microenvironment (TME) that confers resistance to traditional therapies. As the dominant stromal cells in the TME, cancer-associated fibroblasts (CAFs) promote PC progression by modulating the extracellular matrix and interacting with surrounding cells. Numerous PC treatment strategies targeting CAFs have been explored in the past decade. However, targeting different subtypes of CAFs leads to varying therapeutic outcomes, highlighting the intricate and multifaceted nature of CAFs. The heterogeneity and dynamism of CAFs increase the complexity and challenges associated with tumor therapeutics. Currently, combination therapies incorporating CAF-targeted approaches in PC treatment have shown encouraging outcomes in select clinical trials. A comprehensive understanding of CAFs is essential for developing individualized therapeutic approaches. This review outlines the current knowledge of CAF heterogeneity, crosstalk with surrounding cells, and strategies for targeting CAFs in PC, aiming to keep researchers and clinicians up-to-date with the latest information on CAFs in PC.

KEYWORDS Pancreatic cancer; cancer-associated fibroblasts; tumor microenvironment; targeted therapy; heterogeneity

Introduction

Pancreatic cancer (PC) is one of the most lethal malignancies worldwide for which radical resection surgery is the primary curative approach. PC is initially diagnosed at advanced stages owing to the unique anatomic location and vague symptoms with only 25% of patients eligible for surgical intervention. Indeed, optimal treatment selection is pivotal for enhancing PC patient survival[1-3]. Given the limited availability of endorsed therapeutic options for PC, chemotherapy remains the cornerstone of PC treatment. Nevertheless, the inherent resistance of PC to chemotherapy underscores the limited viable treatment options[3-6].

The PC tumor microenvironment (TME) is characterized by a dense desmoplastic stroma that constitutes up to 90% of the tumor volume. The TME is composed of a complex network of cellular and non-cellular components, including cancer-associated fibroblasts (CAFs), immune cells, endothelial cells, and the extracellular matrix (ECM). Among these components, CAFs are among the most abundant and functionally distinct cell types, which have profound effects on tumor biology[1]. Functional analyses have delineated two distinct CAF phenotypes: a pro-tumor M1 phenotype; and an antitumor M2 phenotype. CAFs are known to secrete a wide array of growth factors, cytokines, and ECM proteins, which collectively contribute to tumor growth, invasion, metastasis, and chemoresistance[7,8]. Paradoxically, emerging evidence suggests that some CAF subpopulations may also exert tumor-restraining effects, highlighting the functional heterogeneity and context-dependent roles of CAFs in PC[9,10].

Given the dual roles of CAFs in PC progression and the potential as therapeutic targets, a comprehensive understanding of CAF heterogeneity and functional plasticity of CAFs is essential. This review provides an overview of the current knowledge on CAFs in PC with a focus on the characteristics and emerging therapeutic strategies targeting CAFs in the TME.

Correspondence to: Lei Nie
E-mail: shitouwh@163.com
ORCID ID: https://orcid.org/0000-0002-4373-2506
Received May 28, 2025; accepted September 23, 2025;
published online December 4, 2025.
Available at www.cancerbiomed.org

CAF characteristics

CAF heterogeneity

Studies have described distinct CAF subpopulations. The three most well-characterized CAF subtypes include inflammatory CAFs (iCAFs), myofibroblastic CAFs (myCAFs), and antigen-presenting CAFs (apCAFs)[11,12]. iCAFs and myCAFs represent the principal distinct fibroblast subpopulations in the PC stroma[13]. iCAFs are typically located in hypoxic regions distal to tumor cells and are characterized by elevated expression of fibroblast activation protein (FAP) and inflammatory cytokines, such as IL-6, IL-11, PDGFRα, CXCL12, COL4A1, COL4A2, COL14A1, and leukemia inhibitory factor (LIF), which promote tumor progression and immune suppression[4,14]. CAFs can differentiate into iCAFs induced by IL-1 and TNF-α[15]. myCAFs are enriched in the oxygen-rich areas near well-differentiated cancers[4,13]. Alpha smooth muscle actin (αSMA) is a distinct hallmark of myCAFs. myCAFs also upregulate POSTN, SDC1, COL8A1, COL10A1, COL11A1, and COL12A1 expression[14]. Transforming growth factor (TGF)-β1 is frequently recognized as a conventional inducer of the myCAF phenotype. apCAFs express MHC class II and CD74 invariant chains but lack classical co-stimulatory molecules, such as CD80 and CD86. apCAFs stimulate T cells but also contribute to immune evasion and tumor progression through expression of serum amyloid A3[12]. apCAFs are regulated by interferon (IFN)-γ signaling[12].

In addition to these well-defined subtypes, recent studies have identified novel CAF populations with unique functional properties. Leucine-rich repeat containing 15 (LRRC15)+ CAFs express LRRC15, COL10A1, COL11A1, and MMP11 and are localized around tumor islets[8,16]. Complement-secreting CAFs (csCAFs) express complement components and have tumor-suppressive effects[11]. Metabolic CAFs (meCAFs) are characterized by high expression of group IIA-secreted phospholipase A2 (PLA2G2A), cellular retinoic acid-binding protein 2 (CRABP2), lactate dehydrogenase (LDH) B, and phosphoglycerate kinase 1 (PGK1)[14,17]. The characteristics of the main subtypes are listed in **Table 1**.

CAF roles

CAFs have multifaceted roles in PC progression. One of the most well-established functions of CAFs is an ability to synthesize and remodel the ECM, which provides support and protection for tumor cells and promotes invasion and metastasis[3,18]. CAFs produce a variety of growth factors, cytokines, chemokines, and metabolites that modulate metabolic reprogramming and promote cancer cell proliferation, stemness, and chemoresistance. In addition, CAFs enhance the formation of an immunosuppressive TME by modulating immune cells[10]. Despite predominantly tumor-promoting roles, some CAF subpopulations exhibit tumor-restraining properties. For example, Meflin+ CAFs have been associated with reduced tumor growth and an improved chemotherapy response[19], whereas csCAFs inhibit tumor progression through complement-mediated mechanisms[11]. These divergent functions highlight the importance of context-dependent CAF targeting in therapeutic strategies.

Targeting CAFs for cancer therapy

CAFs influence PC progression in various ways, including cell-to-cell contact, phenotypic conversion, and secretion of paracrine factors or ECM. Interventions that deplete tumor-promoting CAFs, mitigate phenotypic plasticity, disrupt autocrine and paracrine signaling cascades, or target the ECM serve as therapeutic strategies for treating PC. Such strategies aim to attenuate desmoplastic reactions, chemoresistance, and immunosuppression.

CAF depletion

Numerous markers have been identified on CAFs and these markers are not only instrumental in the identification of CAFs but also serve as potential targets for therapeutic interventions. Current strategies for CAF depletion focus primarily on targeting specific CAF subpopulations with FAP+ CAFs representing the main therapeutic targets.

FAP+ CAFs

FAP+ CAFs are predominantly localized in poorly differentiated tumor regions and have been implicated in tumor progression and immune suppression[13]. These FAP+ CAFs contribute to an immunosuppressive TME that is characterized by restricted infiltration of CD8+ T cells[13]. Depletion of FAP+ CAFs has been shown to remodel the ECM, which in turn enhances T-cell infiltration and alleviates T-cell suppression[20]. Depletion of FAP+ CAFs has been shown to suppress tumor growth in KPC mice (an important model for PC) in

Table 1 Characteristics of main subtypes of CAFs in pancreatic cancer

Subtype	Marker	Inducer	Characteristics	Activation pathway
myCAFs	αSMA, POSTN, SDC1, COL8A1, COL10A1, COL11A1, and COL12A1	TGF-β1	ECM remodeling, tumor restraining, adjacent to cancer cells, excluded from hypoxic regions	Hedgehog, ATM signaling, EMT, myogenesis, ECM receptor interaction, and focal adhesion
iCAFs	FAP, IL-6, IL-11, PDGFRα, CXCL12, LIF, COL4A1, COL4A2, and COL14A1	IL-1, TNF-α	Pro-tumor, immunosuppressive, ECM deposition, distant from cancer cells, enriched in hypoxic regions	IL-1-IRAK4, JAK-STAT, and NF-κB signaling
apCAFs	MHC Class II, CD74, and serum amyloid A3	IFN-γ	Anti-tumor, antigen presentation, immune modulation	Antigen presentation and processing, fatty-acid metabolism, MYC targets, and MTORC1 signaling
meCAFs	PLA2G2A, CRABP2, LDHB, and PGK1	NR	Pro-tumor, enriched in loose ECM	NR
LRRC15+ CAFs	LRRC15, COL10A1, COL11A1, and MMP11	TGF-β	Immunosuppression	TGF-β signaling
csCAFs	Complement system components	NR	Anti-tumor	NR

CAFs, cancer-associated fibroblasts; myCAFs, myofibroblastic CAFs; iCAFs, inflammatory CAFs; apCAFs, antigen-presenting CAFs; meCAFs, metabolic CAFs; LRRC15, leucine rich repeat containing 15; csCAFs, complement-secreting CAFs; ATM, mutated in ataxia-telangiectasia; EMT, epithelial mesenchymal transition; ECM, extracellular matrix; αSMA, alpha-smooth muscle actin; TGF-β, transforming growth factor-β; MMP11, matrix metalloproteinases 11; FAP, fibroblast activation protein; LIF, leukaemia inhibitory factor; LDHB, lactate dehydrogenase B; PGK1, phosphoglycerate kinase 1; CRABP2, cellular retinoic acid-binding protein 2; PLA2G2A, group IIA secreted phospholipase A2; NR, not reported; POSTN, periostin; SDC1, syndecan1; PDGFRα, platelet-derived growth factor receptor alpha.

an immune cell-dependent manner. Furthermore, combining depletion of FAP+ CAF with programmed death ligand 1 (PD-L1) or CTLA-4 blockade resulted in synergistic tumor growth inhibition. FAP-IL2v, an antibody against FAP and IL-2 variant, significantly improved the anti-tumor ability of PD-L1 checkpoint inhibition. The triple combination of FAP-IL2v, an anti-PD-L1 antibody, and an excitatory CD40 antibody resulted in excellent anti-tumor activity[21]. Based on preclinical research, FAP-specific chimeric antigen receptor T (CAR-T) cells, which were designed to deplete FAP+ CAFs, effectively inhibited the growth of multiple types of subcutaneously transplanted tumors by increasing endogenous CD8+ T-cell antitumor responses and inhibiting the recruitment of myeloid-derived suppressor cells (MDSCs) without significant off-tumor toxicity[22]. Prior administration of FAP-targeted CAR-T cells significantly potentiated the anti-PC efficacy of CLDN18.2-targeted CAR-T-cells[22] and dual-targeted FAP/CLDN 18.2 CAR-T cells therapy alleviated T-cell exhaustion in a TGF-β-dependent manner[23]. meso^{FAP} CAR-TEAM cells were generated with anti-mesothelin chimeric antigen receptor and a secreted T-cell conjugated molecule that target FAP+ CAFs and recruit T-cells *via* CD3. meso^{FAP} CAR-TEAM cells demonstrated superior efficacy in eradicating PCs and CAFs[24] in a PC mouse model compared to T cells targeting either antigen alone. FAP-based DNA vaccines also eliminate CAFs. The SynCon FAP DNA vaccine, a novel type of tumor antigen-specific vaccine, not only stimulates anti-tumor immunity but also shows synergistic anti-tumor efficacy with other DNA vaccines (**Figure 1A**)[25].

Other options

SMA+ CAFs are abundant in resected samples from patients with non-recurrent PC[26]. However, another study revealed that decreased αSMA+ CAFs correlated with poorly differentiated tumors and poor prognosis[13,27]. Although αSMA+ CAF depletion did not improve the therapeutic efficacy of gemcitabine, αSMA+ CAF depletion increased the effectiveness of anti-CTLA-4 immunotherapy and prolonged animal survival[27]. A higher proportion of LRRC15+ myCAFs in the TME is associated with poor prognosis[16]. Because LRRC15+ CAFs impede CD8+ T cell effector potential, depletion of LRRC15+ CAFs from the PC stroma increases responsiveness to anti-PD-L1 treatment[8]. A subset of myCAFs that exclusively express tryptophan 2,3-dioxygenase (TDO2) promotes

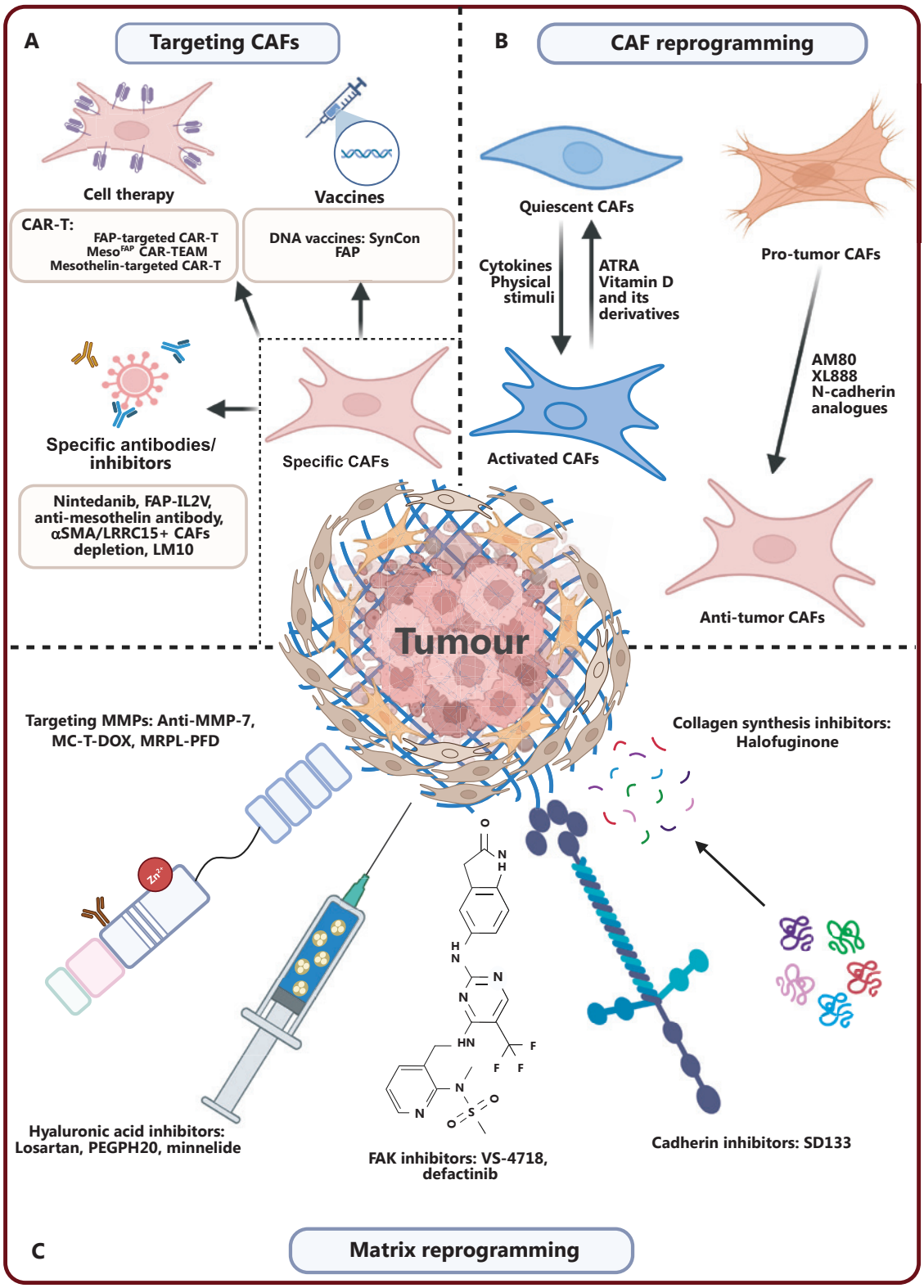

Figure 1 Therapeutic strategies for targeting CAFs in tumors. This schematic illustrates therapeutic strategies for targeting CAFs in tumors, encompassing the following three main modalities: direct depletion of CAFs; alteration of the CAF phenotype; and targeting of CAF-mediated matrix remodelling. (A) Depletion of specific CAF subpopulations. Current CAF-directed therapies can be classified into three principal

categories (vaccines, cell therapy, and specific antibodies). The most advanced vaccine platforms are currently DNA-based, such as the SynCon FAP DNA vaccine, which is designed to elicit immune responses against FAP. CAR-T therapy is the predominant cell-based strategy. Primary targets for CAF-directed CAR-T therapies include mesothelin and FAP. Representative investigational agents include FAP-targeted CAR-T cells, mesothelin-targeted CAR-T cells, and meso^{FAP} CAR-TEAM cells. Additional strategies targeting CAF subsets include nintedanib, FAP-IL2v, anti-mesothelin antibodies, and LM10. Depletion of specific CAF subpopulations, such as αSMA$^+$/LRRC15$^+$ CAFs, is also under investigation. (B) Alteration of the CAF activation status. This strategy seeks to deactivate or reprogram pro-tumor CAFs rather than eliminate pro-tumor CAFs. Pharmacologic agents, such as all-trans retinoic acid, vitamin D, and the analogues, can revert activated CAFs to a quiescent phenotype. Potential agents designed to convert pro-tumor CAFs into anti-tumor CAFs include the synthetic retinoid, AM80, the heat shock protein inhibitor, XL888, and N-cadherin analogues. (C) Targeting CAF-derived ECM. This approach, which aims to remodel the ECM to improve drug delivery and alleviate immunosuppression, consists of five main strategies (inhibition of MMPs, suppression of HA synthesis, inhibition of FAK, disruption of intercellular junctions, and inhibition of collagen synthesis). Representative agents targeting MMPs include anti-MMP-7 antibodies, MC-T-DOX, and MRPL-PFD. Inhibitors of HA synthesis include PEGPH20, losartan, and minnelide. FAK inhibitors, such as VS-4718 and defactinib, represent another therapeutic category. Therapeutics directed at intercellular junctions primarily involve cadherin inhibition, as illustrated by SD133. Halofuginone is a representative inhibitor of collagen synthesis. CAFs, cancer-associated fibroblasts; FAP, fibroblast activation protein; CAR-T, chimeric antigen receptor T-cell; ATRA, all-trans retinoic acid; MMPs, matrix metalloproteinases; FAK, focal adhesion kinase; TDO2, tryptophan 2,3-dioxygenase; αSMA, alpha-smooth muscle actin; LRRC15, leucine-rich repeat containing 15; ECM, extracellular matrix; HA, hyaluronic acid. Figures were created with BioRender software (@biorender.com).

the conversion of CD4+ T cells into Tregs and compromises the activity of CD8+ T cells. The TDO2 inhibitor, LM10, can restore the T-cell anti-tumor response and inhibit the aggressiveness of the cancer[7]. Depletion of PDGFRβ+ CAFs with nintedanib (a multikinase inhibitor) significantly decreased the IL-6 concentration and enhanced the tumor killing efficacy of NK cells. Therefore, a therapeutic strategy combining MSLN-targeted CAR-NK cells and nintedanib may efficaciously ameliorate the clinical outcomes of patients with stroma-rich cancers by modulating the TME[28]. Targeting mesothelin-CAFs also shows promise in the treatment of PC. Anti-mesothelin antibodies effectively reduce the Treg/CD8$^+$ T-cell proportion and inhibit the mesothelial cell-to-apCAF transition, thereby improving immunotherapeutic outcomes[9]. Proton therapy can significantly increase mesothelin expression in tumors. The combination of proton therapy with mesothelin-targeting CAR-T-cell therapy in a flank PC model resulted in superior antitumor growth effects and longer survival than monotherapy. Furthermore, combination treatment in bilateral tumor models can also induce abscopal effects by increasing serum IFN-γ levels and promoting CAR-T cell proliferation (**Figure 1A**)[29].

Reprogramming CAFs into quiescent fibroblasts

CAFs possess cancer-promoting capabilities, whereas quiescent fibroblasts do not exhibit cancer-promoting functions[30]. Pancreatic stellate cells (PSCs) are predominantly quiescent under physiologic conditions. Upon activation by some cytokines and physical stimuli, quiescent PSCs shed cytoplasmic lipid droplets and assume the characteristics of myCAFs.

All-trans retinoic acid (ATRA)

Activated CAFs form a physical barrier to immune cell accessibility, whereas ATRA allows stromal reprogramming through reprogramming of CAFs into quiescent fibroblasts[31]. ATRA has been shown to reduce cell proliferation and migration *via* the Wnt-β-catenin signaling pathway[32]. ATRA as a standalone treatment does not affect the progression of PC. However, when combined with gemcitabine and other chemotherapy drugs, ATRA significantly inhibits tumor growth. A phase Ib trial successfully established the safety and tolerability of ATRA in combination with gemcitabine and nab-paclitaxel in patients with PC. This treatment strategy showed promise in increasing the concentration of intratumoral chemotherapy agents while reducing adverse drug reactions[31]. Notably, ATRA treatment has also been demonstrated to increase T-cell infiltration, resulting in prolonged survival in KPC mice.

Vitamin D and its derivatives

Studies have shown that vitamin D (VD) receptor (VDR) expression is very high in CAFs. VDR is the principal regulator of CAFs. VDR ligands can enhance the chemotherapeutic response by inducing stromal remodeling. Multiple studies have shown that VD and VD derivatives promote the conversion of activated CAFs to a quiescent state. However, Gorchs[33] reported that VD has the following dual effects: VD decreases

the release of pro-tumorigenic substances, such as prostaglandin E2, IL-6, and periostin, in iCAFs; and VD reduces T-cell mediated tumor immune surveillance. A clinical study involving 68 patients revealed that higher plasma VD levels were associated with longer progression-free survival (PFS) and VD supplementation may be beneficial for the prognosis of PC in patients through suppression of CAFs[34]. The VD analogue, seocalcitol (EB1089), alone did not show objective anti-tumor activity in advanced PC in a phase II trial[35]. A phase II pilot trial combining the VD analogue, paricalcitol, with cisplatin, gemcitabine, albumin bound paclitaxel, and nivolumab showed promising results for patients with metastatic PC[36].

Other options

Another study involving 71 human PCs revealed that infiltration of Meflin+ CAFs was positively correlated with favorable patient outcomes and Meflin ablation resulted in significant tumor progression with poorly differentiated histology, whereas Meflin overexpression suppressed tumor growth in mouse models. Thus, Meflin+ CAFs are regarded as anti-tumor CAFs[19]. The synthetic non-natural retinoic acid, AM80, can convert Meflin− CAFs to Meflin+ CAFs. Whether AM80 enhances the efficacy of cancer drugs against advanced PC is undergoing evaluation in an open-label phase I/II clinical trial[37]. Zhang[30] reported that the mechanical binding of N-cadherin and HAVDI (an N-cadherin ligand) leads to transformation of activated CAFs to a quiescent state, providing a foundation for the development of novel therapeutic approaches. Treatment of primary patient CAFs with the Hsp90 inhibitor, XL888, effectively inhibits the iCAF phenotype by inhibiting JAK/STAT activity. Combined therapy with XL888 and anti-programmed death receptor 1 (PD-1) significantly increased CD8+ T-cell infiltration and prolonged the survival time of C57BL/6 mice bearing syngeneic subcutaneous or orthotopic tumors (**Figure 1B**)[38].

Targeting the CAF-derived ECM

CAFs produce various types of collagen and hyaluronic acid (HA) that contribute to the composition of the ECM. ECM remodeling acts as a physical barrier that prevents anti-tumor immune cells and therapeutic drugs from killing tumor cells. Therefore, targeting the proteins in the ECM or breaking down the ECM could be a potential therapeutic approach. Studies have shown that anti-ECM therapy has dual effects. Specifically, some studies have indicated an improved treatment response, while other studies pointed to potential drawbacks, such as increased tumor progression and metastasis.

Type I collagen

αSMA+ CAFs are major producers of type I collagen (Col1) in the PC matrix[39]. The Col1 synthesis inhibitor, halofuginone, significantly affects the TME in PC. Specifically, halofuginone leads to enhanced infiltration of the immune system into areas characterized by low levels of HA. Consequently, this infiltration results in a greater abundance and wider dispersion of both classically activated inflammatory macrophages and cytotoxic T cells[40]. Deletion of Col1 in myCAFs was shown to accelerate PC progression and decrease survival in a dual-recombinase genetic mouse model of spontaneous PC by promoting MDSC recruitment and impeding the infiltration of CD8+ T cells, which are attenuated by the combined inhibition of CXCR2 and CCR2[39].

HA

HA produced by CAFs is a major source of intratumor stromal pressure. HA synthase 1 and some collagens are expressed at higher levels in iCAFs, indicating that HA synthase 1 and some collagens have specific roles in synthesis of the ECM[12]. Most of the available clinical studies involving PC have focused on the effects of PEGPH20 in combination with cytotoxic drugs. A phase II study (HALO 202) reported that the combination of PEGPH20 plus gemcitabine and nab-paclitaxel significantly improved PFS in patients with PC and high HA expression[41]. However, a further phase III trial (HALO 109-301) revealed that this regimen did not improve the primary endpoint, overall survival (OS)[42]. A preclinical study indicated that minnelide, a water-soluble prodrug of triptolide (an active compound from a Chinese herb) not only reduced HA and collagen in mouse models but also enhanced vascular function and drug delivery within the tumor. The synergistic effect between minnelide and conventional chemotherapy not only significantly reduced the dosage of these toxic drugs but also effectively enhanced the therapeutic outcome against cancer and the stromal components[43]. In addition, several ongoing clinical studies are further investigating the potential of minnelide. The angiotensin inhibitor, losartan, has been shown to reduce the production of interstitial HA. Losartan, in combination with FOLFIRINOX and chemoradiation, led to an improved OS for patients with PC by decreasing the number of Tregs and increasing the number of CD8+ T cells[44].

Focal adhesion kinase (FAK)

FAK is associated with ECM stiffness in PC. FAK activity in CAFs is an independent predictor of poor prognosis and tumor-infiltrating cytotoxic T cells. The FAK inhibitor, VS-4718, diminishes ECM remodeling, increases responsiveness to chemotherapy, and enhances sensitivity to immunotherapy. Notably, combining the FAK inhibitor, VS-4718, with checkpoint immunotherapy and radiotherapy or chemotherapy was reported to result in tumor eradication[45]. A phase 1b/2 study confirmed the safety and efficacy of an FAK inhibitor (defactinib) and the RAF/MEK clamp inhibitor (avutometinib) in combination with gemcitabine and nab-paclitaxel as first-line treatments for metastatic PC[46].

Matrix metalloproteinases (MMPs)

Activated MMPs contribute to ECM degradation, thus overcoming the physical limitations of cell movement, which is involved in tumor invasion. MMPs may be preferable antitumor targets. Upregulation of membrane type 1-matrix metalloproteinase (MT1-MMP) contributes to increased resistance to gemcitabine in PC and MC-T-DOX is a synthetic liposome designed for tumor-targeted drug delivery. MC-T-DOX enhances intratumoral vascular density upon activation by MT1-MMP, thereby improving drug penetration and accumulation within the tumor[47]. Anti-MMP-7 also increases the sensitivity to chemotherapy, which enhances apoptosis of cancer cells[48]. However, the results of clinical studies on MMP targeting have not shown benefits for PC[49,50]. A pirfenidone-loaded, MMP2-responsive peptide-hybrid liposome (MRPL-PFD) has been exploited for drug delivery purposes and tumors treated with therapeutic MRPL-PFD were shown to have better drug penetration and lower Col1 and fibronectin levels. Importantly, the tumor volume was greatly reduced[51].

One study revealed that loss or inhibition of cadherin 11 resulted in a significant decrease in the expression of ECM components. SD133, a small molecule inhibitor of cadherin 11, effectively attenuated tumor growth and prolonged survival in KPC mice during the treatment period (**Figure 1C**)[52].

Targeting signaling in CAFs

Studies have demonstrated the critical role of IL-1 receptor-associated kinase 4 (IRAK4)/NF-κB, LIF, IL-6/STAT3, TGF-β, CXCL12/CXCR4, hedgehog (HH), and hepatocyte growth factor (HGF)/c-MET signaling in CAF activation.

IL-1/NF-κB signaling

IL-1 expression, which is associated with poor survival in PC patients, critically activates IRAK4 in CAFs, leading to fibrosis, metastasis, chemoresistance, and immunosuppression[53]. A study (NCT02021422) is being launched involving anakinra, a human IL-1 receptor antagonist, in combination with standard chemotherapy for treating PC. Conditional deletion or pharmacologic inhibition of IRAK4 reduces the levels of immunosuppressive cytokine expression (IL-6, IL-8, CXCL2, and CXCL5)[54], reduces NF-κB activity, decreases tumor desmoplasia, increases the activity of infiltrating CD4+ and CD8+ T cells; an antitumor phenotype of CAFs was observed[54]. NF-κB signaling modulates IL-1-induced IL-6 secretion[55] and is a key regulator of the acquisition and maintenance of the tumor-promoting functions of iCAFs. The gene expression profile of iCAFs was attenuated after treatment with an NF-κB small-molecule inhibitor[15,56]. Garg[57] demonstrated that co-injection of orthotopically implanted KPC tumors with fibroblasts with a deletion of the p50 subunit of NF-κB reduced tumor volume and prolonged animal survival by increasing cytotoxic T-cell tumor infiltration.

LIF signaling

LIF overexpression drives iCAF phenotype *via* activation of the JAK-STAT signaling cascade. A clinic study revealed that the LIF protein is associated with poorly differentiated tumors. Pharmacologic blockade or genetic deletion of LIF inhibited tumor progression and enhanced the efficacy of chemotherapy in PC mouse models[58]. A phase I dose escalation trial demonstrated that the LIF monoclonal antibody, MSC-1, has favorable safety and efficacy profiles in patients with advanced solid tumors. Furthermore, the unique attributes of MSC-1 in modulating the TME suggest promising opportunities for synergistic combinations with additional therapeutic agents[59]. JAK inhibition resulted in a reduction in tumor volume and an increase in the number of myCAFs in KPC mice. Ruxolitinib, a JAK1 and JAK2 inhibitor, has also undergone clinical evaluation for efficacy in treating PC. Although ruxolitinib improved OS in the randomized phase II RECAP study, ruxolitinib failed to prolong OS in two randomized phase III studies[60].

IL-6/STAT3 signaling

Elevated serum IL-6 levels are a predictor of poor survival in patients with PC. IL-6 is a key regulator of STAT3 activation in cancer cells and is a primary driver of tumor cell survival and resistance to treatment[61]. IL-6 interacts with membrane-bound IL-6R and activates JAK/STAT3 *via* gp130. IL-6 deletion in

CAFs was reported to modulate the TME in genetically engineered mouse models of PC, improve chemotherapy efficacy, and synergize with checkpoint blockade therapy[28]. A trial using an anti-IL-6R monoclonal antibody (RoActemra) demonstrated significant suppression of PC progression *in vivo*[62]. Enhanced tumor regression and increased OS were detected in mice treated with anti-IL6Ralpha antibody and gemcitabine[61]. Raloxifene not only directly binds to gp130 and forms a complex with the IL-6 receptor to suppress the JAK/STAT3 pathway but also inhibits IL-6 synthesis, thereby inhibiting PC progression *in vitro* and in orthotopic PC xenografts[63]. Because IL-6 targets the tumor-immune interface of PC, combined IL-6 and PD-L1 blockade elicits significant antitumor activity and increases OS in orthotopic mouse xenograft models of PC[64]. The addition of MEK and STAT3 inhibitors to PD-1 blockade not only improves OS in PKT mice (a genetically-engineered mouse model of PC in which cells expressing αSMA are ablated owing to the induction of thymidine kinase by ganciclovir administration) but enhances the cytotoxic effect of T cells in the TME by attenuating myCAFs. Importantly, the combination of an MEK inhibitor (trametinib), a STAT3 inhibitor (ruxolitinib), and a PD-1 inhibitor (nivolumab) provide clinical benefits for patients with chemotherapy-resistant PC[65].

TGF-β signaling

Blockade of TGF-β signaling demonstrated the therapeutic efficacy against CAFs. The combination of the TGF-β receptor I kinase inhibitor, galunisertib, with durvalumab demonstrated good tolerability in patients with PC treated with ≤2 systemic regimens in a single-arm, multinational, phase Ib study. However, the clinical activity warrants further study[66].

CXCL12/CXCR4 signaling

FAP+ CAFs are the principal source of CXCL12 in the TME of patients with PC. Activation of the CXCL12/CXCR4 signaling pathway not only promotes the progression and angiogenesis of PC but also mediates immune escape. Preclinical studies revealed that CXCL12/CXCR4 signaling pathway blockade converts the TME from "cold" to "hot" by enhancing T-cell infiltration[60]. Administration of the CXCR4 inhibitor, AMD3100, acts synergistically with immunotherapy antibodies to enhance the antitumor effects. Among 29 patients with PC who received the CXCR4 antagonist, BL-8040, and pembrolizumab as second-line therapy, the disease control rate and median OS were 34.5% and 7.5 months, respectively[5]. The combination of BL-8040, pembrolizumab, and chemotherapy was shown to be safe and well-tolerated and achieved therapeutic benefit in patients with *de novo* metastatic PC and disease progression on front-line gemcitabine-based therapy in the COMBAT/KEYNOTE-202 trial[67]. A phase I/II clinical trial demonstrated that the CXCL12 inhibitor, NOX-A12, combined with pembrolizumab is safe and increases immune cell infiltration in the PC TME[68]. These results indicated that blocking the expression of CXCL12/CXCR4 and PD-1 may increase the anti-tumor effect of chemotherapy.

HH signaling

HH signaling is aberrantly expressed in CAFs[69]. HH inhibition modulates the TME by affecting ECM-related gene expression, downregulating cytokine secretion by CAFs, and altering CAF subtypes. HH inhibition using genetic or pharmacologic approaches in KPC mice, such as IPI-926 and patched 1-interacting peptide, leads to fibroblast depletion, suppresses fibrosis, reduces survival time, decreases tumor differentiation and increased vascularity[70]. Conversely, activation of HH using agonists increases CAF proliferation, promotes stromal hyperplasia, and attenuates tumor growth[71]. Another study demonstrated that the HH inhibitor, sonidegib (LDE225), enhances the sensitivity of PC tumors to chemotherapy in mouse models[72]. HH depletion does not enhance the efficacy of gemcitabine in the treatment of PC but effectively improves tumor sensitivity to VEGFR inhibitors or anti-CTLA4 immunotherapy[27]. Catenacci reported that vismodegib neither enhanced drug delivery nor treatment efficacy in a randomized phase Ib/II study involving patients with metastatic PC gemcitabine plus placebo or the HH inhibitor, vismodegibin and addition of vismodegib to gemcitabine did not improve the objective response rate (ORR), progression-free survival (PFS), or OS[69].

Insulin-like growth factor 1 (IGF1) signaling

HH upregulates the secretion of IGF1 and GAS6 in myCAFs, which activate the respective receptors, the IGF1 receptor (IGF-1R), and AXL, thereby activating AKT signaling. Pharmacologic inhibition of IGF-1R and AXL *in vitro* reverses the pro-tumor phenotypes of myCAFs but inhibition of IGF-1R or AXL only has a limited effect on decreasing tumor burden[73]. However, the selective AXL kinase inhibitor, BGB324, enhances the efficacy of gemcitabine by modulating the immunologic landscape[6]. A recent study revealed that an AXL inhibitor (TP-0903) exhibits antitumor properties and enhances the effectiveness of other therapies in preclinical models of PC[74]. TP-0903 is currently undergoing clinical trials for solid tumors (NCT02729298). A randomized, phase I/II

study that focused on the safety, tolerability, and outcomes of the IGF-1R antagonist, MK-0646, in combination with gemcitabine for advanced PC demonstrated that the combination of MK-0646 plus gemcitabine was tolerable and improved OS but not PFS[75]. Ganitumab, a monoclonal antibody targeting IGF-1R, showed acceptable toxicity and demonstrated potential clinical efficacy in a randomized phase II study. However, the phase III randomized, double-blind, placebo-controlled trial assessing ganitumab in combination with gemcitabine was terminated because the primary analysis indicated a negative outcome[76]. In an international, randomized, double-blind, placebo-controlled phase II study involving untreated metastatic PC, adding istiratumab, an IGF1R and ErbB3 bispecific antibody, to standard chemotherapy failed to improve the ORR and OS[77]. A phase Ib/II study revealed that combining the IGF-1R inhibitor, cixutumumab, with erlotinib and gemcitabine in treatment-naïve patients with metastatic PC failed to improve patient survival[78].

HGF/c-MET signaling

Overexpression of HGF/c-MET in CAFs stimulates PC cell growth and is associated with a poor prognosis[79]. Treatment with the HGF neutralizing antibody, rilotumumab (AMG102), reduced the volume of the PC in mouse models and demonstrated efficacy comparable to conventional chemotherapy in impeding tumor growth[80]. Crizotinib, an MET inhibitor, has been shown to prevent peritoneal metastasis of PC[81]. The c-MET antibody, emibetuzumab, in combination with erlotinib proved to be a safe treatment for PC in a phase I trial[82]. A combined approach using HGF/c-MET inhibitors and chemotherapy effectively decreases tumor burden and eliminates metastasis[83]. A phase I clinical trial investigated the effect of the c-Met inhibitor, cabozantinib, on the efficacy of gemcitabine for treating PC but the sample size was small and continuous adverse reactions occurred[84]. These findings provided a strong platform for the assessment of this triple therapy approach in the clinical setting[85]. Another study has indicated that blocking HGF, c-MET, and urokinase-type plasminogen activator (uPA) can diminish the angiogenic properties of endothelial cells, underscoring the influence of CAFs and the HGF/c-MET pathway on neoangiogenesis[86]. Further studies on the role of c-Met inhibition in PC may be needed.

Other pathways

CAFs can accelerate the invasion and migration of PC through the chemokine-receptor axis[87]. Blocking the CXCL/CXCR2 axis results in alterations in the TME, which is characterized by reduced infiltration of neutrophils, MDSCs, and arginase-1+ macrophages[87]. CXCL3/CXCR2 signaling can promote the transformation of CAFs to myCAFs[88]. A study demonstrated that the CXCR2/1 small-molecule antagonist, SCH-479833, has both anti-tumor and anti-metastatic effects in mouse models[89]. Another study revealed that inhibition of CXCR2 reversed tumor progression promoted by Col1 deletion in a PC mouse model[39]. CCL26, which can be induced by nab-paclitaxel in iCAFs, can enhance the invasiveness of PC through the PI3K/AKT/mTOR pathway and blocking the PI3K/AKT pathway can reverse CCL26-induced invasion and migration in PC[90]. CCL2 secreted by CAFs creates an immune-suppressive TME. A phase Ib study revealed that PF-04136309, an oral small-molecule CCR2 (CCL2 receptor) inhibitor, increased the sensitivity of PC to FOLFIRINOX chemotherapy[91] but failed to increase the efficacy of nab-paclitaxel/gemcitabine in another phase Ib study (**Figure 2**)[92].

Additional therapeutic targets in CAFs

Metabolic reprogramming

Metabolic reprogramming is one feature of the acquisition of tumor-promoting function by CAFs. Recent experiments have shown that CAFs affect the metabolism of cancer. Cancer cells undergo a process known as the "Warburg effect" in the TME, where cancer cells convert pyruvate into lactate when there is sufficient oxygen. The excess lactic acid produced by cancer cells is transported to the TME *via* the lactic acid transporter monocarboxylic acid transporter (MCT) 4, which is utilized by CAFs *via* MCT1, thereby eliminating lactic acid from the TME[93,94]. CAFs can directly feed cancer cells by secreting lactate and pyruvate in a manner that relies on the "reverse Warburg effect." Cancer cells transform CAFs into factories that produce energy-rich metabolites for tumor progression in this scenario. CAFs undergo metabolic reprogramming and engage in glycolysis under hypoxic conditions, in which CAFs export lactate to tumor cells for oxidative phosphorylation[93]. LDH is highly expressed in CAFs[95]. The expression of LDH, which regulates lactate generation, has been identified as a poor prognostic factor in PC patients. Niftimox, an inhibitor of LDH, augments the responsiveness of PC to chemotherapy and immunotherapy *via* inhibition of the JAK1/STAT1 pathway and suppression of the recruitment and function of CXCR2+ neutrophils[96]. Depletion of LDH A inhibits tumor growth. Lactate-stimulated CAFs upregulate IL-6 expression

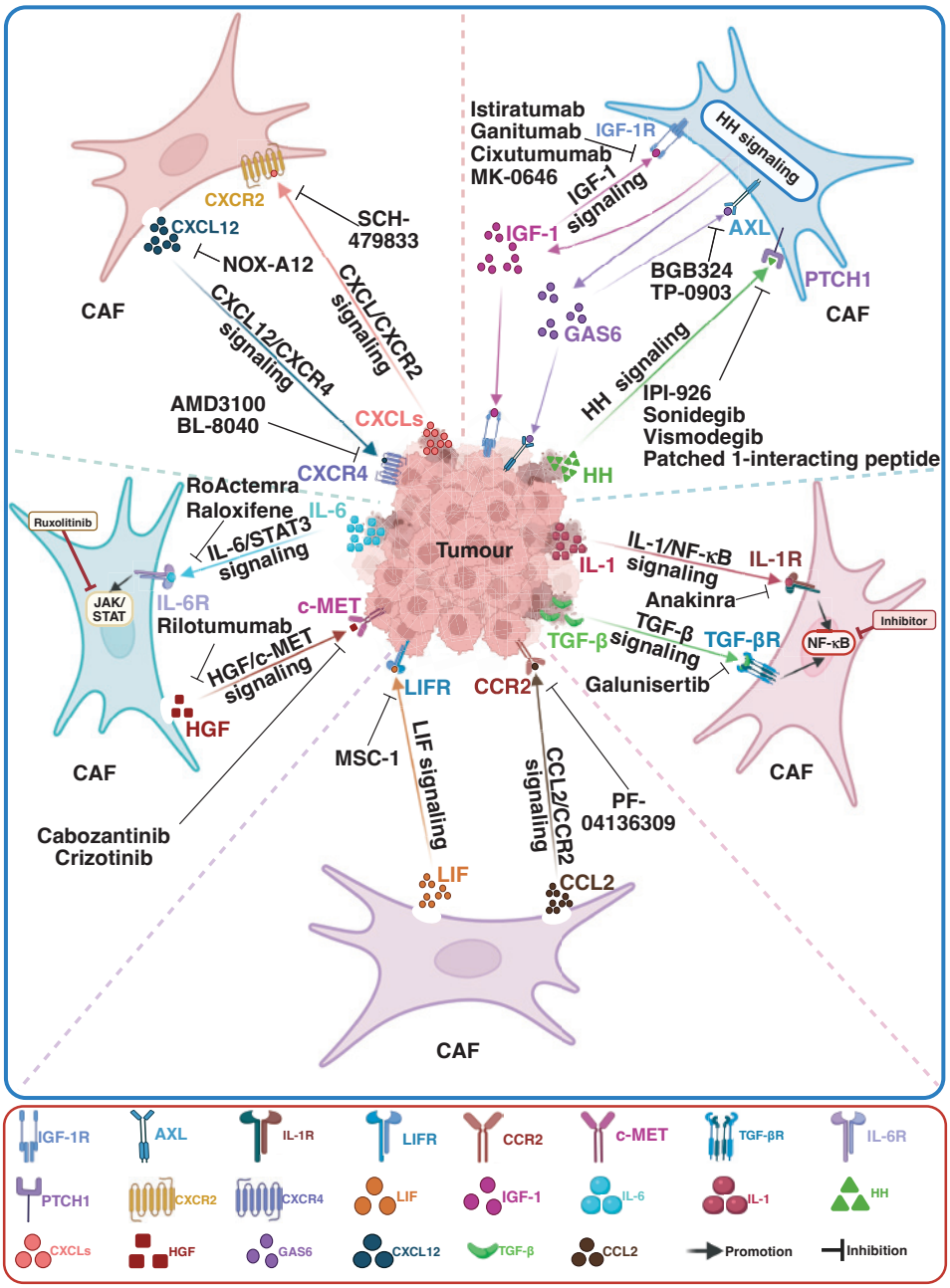

Figure 2 Targeting key signaling pathways in CAFs. Targeting key signaling pathways that mediate the bidirectional crosstalk between CAFs and tumor cells represents a promising therapeutic strategy. These functional interactions are facilitated through multiple molecular axes, including the IGF-1, HH, IL-1/NF-κB, TGF-β, CCL2/CCR2, LIF, HGF/c-MET, IL-6/STAT3, CXCL12/CXCR4, and CXCL/CXCR2 signaling pathways, which promote tumor cell survival, proliferation, migration, and CAF activation. Corresponding inhibitors against these pathways have now been developed and are under investigation in clinical or preclinical trials. These inhibitors include istiratumab, cixutumumab, ganitumab, MK-0646, BGB324, and TP-0903 against IGF-1 signaling; IPI-926, sonidegib (LDE225), vismodegib, and a patched 1-interacting peptide targeting HH signaling; anakinra, which blocks IL-1/NF-κB signaling; galunisertib, which modulates TGF-β signaling; PF-04136309, which targets the CCL2/CCR2 axis; MSC-1, an inhibitor of LIF signaling; rilotumumab (AMG102), cabozantinib, crizotinib, and emibetuzumab, which target the HGF/c-MET axis; RoActemra and raloxifene, which inhibit IL-6/STAT3 signaling; NOX-A12, AMD3100, and BL-8040, which target CXCL12/CXCR4 signaling; and SCH-479833, which inhibits the CXCL/CXCR2 axis. CAFs, cancer-associated fibroblasts; IGF1, insulin-like growth factor 1; HH, Hedgehog; LIF, leukaemia inhibitory factor; TGF-β, transforming growth factor β; HGF, hepatocyte growth factor. Figures were created with BioRender software (@biorender.com).

and cooperate with lactate to suppress cytotoxic immune cell activity. The LDH A inhibitor, FX11, reduces the tumor growth rate and increases the abundance of CD8+ T and NK cells expressing granzyme B and IFN-γ in a CAF-rich murine PC model[97]. The TGF-β-SMAD5 axis promotes protein turnover flux in iCAFs and proteins secreted by CAFs support biological processes leading to cancer progression[18]. Studies have also demonstrated that TGF-β1 accumulation accelerates aerobic glycolysis and promotes the transport of lactic acid out of CAFs *via* MCT4[98]. The metabolic crosstalk between CAFs and tumor cells is interrupted when MCT1 or MCT4 is blocked and pharmacologic targeting of MCT1 or MCT4 is being pursued as an anticancer therapy. AZD3965, a small-molecule inhibitor of MCT1, resulted in lactate accumulation and significant tumor growth inhibition in a Raji Burkitt's lymphoma model[99]. In a multicenter, phase I dose-escalation and dose-expansion trial, AZD3965 also showed safety and tolerability in patients with advanced solid tumors[100]. Shikonin enhances PC sensitivity of PC to gemcitabine *via* suppressing reverse Warburg effect in CAFs[101]. Syrosingopine, a dual MCT1 and MCT4 inhibitor, results in glycolytic blockade, intracellular lactic acid accumulation, and synthetic lethality in tumor cells[102].

Caveolin-1 (CAV1) serves as a biomarker for the "reverse Warburg effect." CAV1 deficiency in CAFs has been shown to increase the levels of glycolytic enzymes. A reduction in CAV1 in fibroblasts is associated with activation of TGF-β signaling, which leads to the intracellular accumulation of alpha-ketoglutaric acid through inhibition of isocitrate dehydrogenase 1 (IDH1)[103]. IDH1 promotes PC resistance to chemotherapy by promoting mitochondrial function and the production of alpha-ketoglutaric acid and NADPH to neutralize reactive oxygen species. Anti-IDH1 therapy combined with conventional therapy has demonstrated efficacy in treating PC *in vitro* and *in vivo*[104]. A trial focusing on the safety and efficacy of the IDH1 inhibitor, ivosidenib, in combination with modified FOLFIRINOX is ongoing in PC (NCT05209074).

Metabolic stress caused by hypoxia, nutrient deficiency, and a stiffened stroma promotes autophagy, which promotes tumor growth in a variety of ways, such as promoting the secretion of nucleosides by CAFs that facilitate glucose metabolism and growth by cancer cells[105]. Netrin G1 (NetG1)-expressing CAFs secrete nutrients, such as glutamate and glutamine, which can be utilized by PC cells under regulation by NGL-1[106]. Bai and colleagues[107] reported that autophagy activates CAFs by promoting proline biosynthesis and collagen production. Inhibiting mitophagy by targeting PRKN, a crucial enzyme that regulates mitochondrial autophagy, reduces the tumor burden[107]. The autophagy inhibitor, chloroquine, can effectively enhance the therapeutic effect of gemcitabine on PC[3]. Cancer-stimulated CAFs secrete alanine through the transporter, SLC1A4, in an autophagy-dependent manner, whereas cancer cells upregulate the transporter, SLC38A2, to transfer alanine into the cells as an alternative carbon source. Targeting SLC38A2 leads to an intratumor redox crisis and inhibits tumor growth in PC mouse models[108].

CAFs also promote tumor progression by providing lipids. Lysophosphatidylcholines (LPCs) secreted by CAFs are crucial components of cancer cell membranes. In addition, cancer cells secrete autotaxin, a lysophospholipase enzyme, which hydrolyses LPC into lysophosphatidic acid, promoting PC proliferation and migration through the AKT signaling pathway. These lipid-rich CAFs are then able to supply lipids to cancer cells for mitochondrial oxidative phosphorylation through the ABCA8a transporter[109]. CAFs can facilitate communication between cells or between cells and the ECM through the production of S-type lectins. Galectin-1, a specific lectin, has a role in inducing apoptosis in T cells by binding to CD7 and CD45 present on the T-cell surface[110]. Furthermore, galectin-1 is highly expressed in regulatory T cells and is involved in the immunosuppressive function[110]. The Na+/H+ exchanger, NHE1, as the major acid extruder in CAFs, has a crucial role in the maintenance of myCAFs phenotype in a harsh acidic TME[94]. Inhibition of NHE1 on the membrane of CAFs with cariporide (a selective inhibitor of the NHE1 protein) decreases the proportion of myCAFs in PCs. This effect leads to a reduced desmoplastic reaction. Adjuvant PC therapy with an NHE1 inhibitor reduces desmoplasia, shifting the immune cell infiltration from a largely innate immune cell-rich state to a more lymphocytic infiltration state (**Figure 3**)[94].

Hypoxic TME

Intratumoral hypoxia is a typical hallmark of PC. Recent discoveries demonstrated that hypoxia promotes tumor aggressivity and therapeutic resistance. Hypoxia signaling is stabilized by hypoxia-inducible factors (HIFs). Increased ROS production by hypoxic cancer cells induces oxidative stress in CAFs and promotes autophagy and HIF-1α stabilization. High levels of hypoxic ROS are essential for HIF-1α stabilization. HIF-1α stabilization in CAFs has a key role in

promoting an inflammatory phenotype. Resveratrol significantly inhibits the hypoxia-stimulated production of ROS and HIF-1α in a concentration-dependent manner, thus inhibiting the progression of PC. N-acetylcysteine, a scavenger of ROS, inhibits hypoxia-driven ROS-induced cancer progression[111]. CAF-secreted metabolites fuel the biosynthetic pathways of cancer cells[112]. Hypoxia promotes the secretion of high levels of miR-21 extracellular vesicles by CAFs through the HIF-1α/miR-21 axis and miR-21 extracellular vesicles trigger the maintenance of PC stemness and gemcitabine resistance *via* the RAS/AKT/ERK pathway[113]. HIF2 might also be a target for myCAFs, as evidenced by a study that reported deletion of HIF2 in myCAFs dramatically decreases the intratumoral recruitment of Treg cells and immune-suppressive M2 macrophages. Treatment with the therapeutic HIF2 inhibitor, PT2399, significantly decreased *in vitro* macrophage chemotaxis and M2 polarization in PC animal models and enhanced the therapeutic efficacy of immunotherapy in syngeneic PC mouse models[1].

Targeting hypoxic areas with novel therapeutic approaches may offer additional anti-tumor activity and clinical benefits beyond conventional treatments. Evofosfamide is a prodrug that can be activated in hypoxic environments and induce tumor cell death. An animal study revealed that evofosfamide not only kills hypoxic PC cells but also enhances the efficacy of radiotherapy and chemotherapy[114]. The combination of evofosfamide with gemcitabine significantly improves the PFS of patients with locally advanced or metastatic PC in a randomized phase II trial compared to gemcitabine alone[115]. Systemic administration of hypoxia inducers (evofosfamide and sunitinib) to 17 patients with advanced or metastatic unresectable pancreatic neuroendocrine tumors resulted in an ORR of 17.6% and a median PFS of 10.4 months[116].

VEGF released by hypoxic CAFs *via* the HIF pathway regulates pathologic angiogenesis and vascular permea-bility in patients with PC. VEGFR inhibitors have been proposed for the treatment of PC and many clinical trials have been subsequently conducted. Although many phase I trials on VEGFR have shown encouraging results[117], the results of subsequent phase II/III trials have been mostly unsatisfactory. A Japanese multicenter, double-blind clinical trial used gemcitabine plus elpamotide (VEGFR 2 peptide) for PC but gemcitabine plus elpamotide failed to extend the PFS and OS[118]. Theoretically, anti-angiogenic therapy for PC can inhibit tumor proliferation and metastasis but the results are controversial (**Figure 3**).

Perspectives and conclusions

The crucial role of CAFs in PC progression is increasingly recognized. Previous studies have indicated that targeting CAFs not only remodels the TME and enhances intratumoral drug concentration but also potentiates the efficacy of therapeutic modalities, such as chemotherapy or immunotherapy. Consequently, drug discovery efforts directed against CAFs offer promising therapeutic prospects for the treatment of PC.

As dynamic components of the TME, CAFs exhibit context-dependent phenotypic plasticity. Despite the proposed biomarkers, the absence of definitive subtype-specific markers and clinically viable methods for real-time phenotypic monitoring critically hinders targeted therapeutic development[15]. CAF heterogeneity further complicates the multifaceted interactions with surrounding cells. Delineating the mechanisms underlying the role of CAF heterogeneity in PC development and establishing precise identification methods for pro-tumorigenic CAF subsets would significantly advance both biological understanding and therapeutic innovation[10]. As novel genetically engineered mouse models emerge to elucidate the functional heterogeneity of CAFs, research interests are increasingly shifting towards therapeutic modulation of the pro-tumorigenic phenotypes. For example, strategies targeting NetG1, autophagy-dependent metabolic reprogramming, or the hypoxic TME have shown potential in altering CAF behavior[106]. However, clinical translation remains challenging. For example, HH inhibitors demonstrate limited patient benefit and collagen-targeting approaches have yielded paradoxical results. This finding may reflect underlying tumor heterogeneity, including variable target protein expression, inadequate drug penetration, rapid phenotypic plasticity of CAFs, upregulation of multidrug resistance proteins, metabolic reprogramming, and an immunosuppressive TME[2]. While monotherapies targeting specific CAF subpopulations have shown limited survival benefits in patients with PC, current research predominantly focuses on multidrug combination strategies (**Table 2**). In addition to the anti-tumor potential, the potential of CAF-directed interventions to ameliorate systemic symptoms (pain, cachexia, and fatigue) warrants further investigation[119].

Advances in artificial intelligence could enable machine learning-driven integration of multiomics data, including

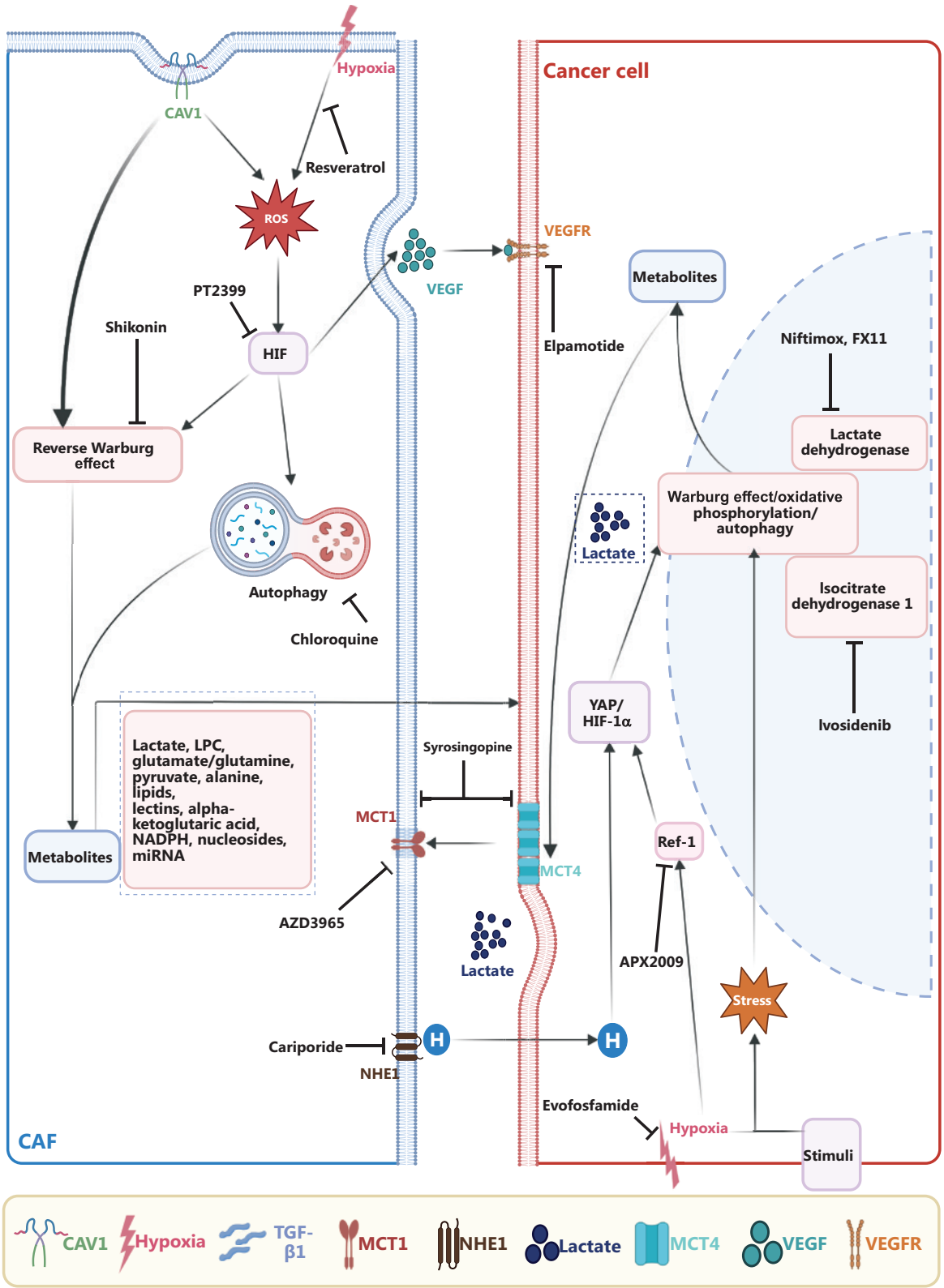

Figure 3 Targeting hypoxia and metabolic reprogramming. CAFs support metabolic reprogramming in tumor cells under hypoxic and nutrient-deprived conditions. CAFs can provide nutrients to cancer cells through various mechanisms, thereby promoting their survival.

Key mechanisms include hypoxia and aberrant CAV1 expression, which promote ROS production and subsequently induce HIF activation. Accumulated HIF facilitates tumor growth *via* VEGF production and supplies cancer cells with abundant metabolic substrates through metabolic reprogramming, such as the reverse Warburg effect and autophagy, thereby nourishing the tumor. Moreover, acidosis within CAFs can regulate cancer cell metabolism. Under hypoxic conditions, cancer cells undergo metabolic reprogramming and produce metabolites, such as lactate, which in turn influence CAF metabolism and modulate the CAF phenotype. Strategies targeting hypoxia and metabolic reprogramming have emerged as promising therapeutic strategies. This approach can be categorized into the following three principal classes: agents targeting hypoxia, including the ROS synthesis inhibitor, resveratrol, the hypoxic microenvironment-targeting prodrug, evofosfamide, and the angiogenesis modulator, elpamotide; compounds targeting metabolic reprogramming, such as the reverse Warburg effect inhibitor, shikonin, the autophagy inhibitor, chloroquine, the lactate dehydrogenase inhibitors, niftimox and FX11, the Ref-1 inhibitor, APX2009, and the isocitrate dehydrogenase 1 inhibitor, ivosidenib; and inhibitors targeting metabolite transport, such as the MCT inhibitors, syrosingopine and AZD3965, and the NHE1 inhibitor, cariporide. CAFs, cancer-associated fibroblasts; CAV1, caveolin-1; HIF, hypoxia-inducible factor; NHE1, Na^+/H^+ exchanger 1; MCT, monocarboxylic acid transporter; ROS, reactive oxygen species. Figures were created with BioRender software (@biorender.com).

Table 2 Selected ongoing clinical trials targeting CAFs

Target	Drug	Combination therapy	Identifies	Status	Phase
FAP+ CAFs	FAP-CAR-T	Monotherapy	NCT03932565	Unknown	Phase I
	MP0317	Monotherapy	NCT05098405	Terminated	Phase I
	OMTX705	Pembrolizumab	NCT05547321	Recruiting	Phase I
	177Lu-LNC1004	Monotherapy	NCT05723640	Recruiting	Phase I
Mesothelin+ CAFs	huCART-meso cells	Chemotherapy	NCT03323944	Recruiting	Phase I
Hyaluronic acid	Losartan	Nab-paclitaxel, gemcitabine	NCT05861336	Active, not recruiting	Phase II
		Nivolumab, FOLFIRINOX, and stereotactic body radiotherapy	NCT03563248	Active, not recruiting	Phase II
	PEGPH20	Gemcitabine, nab-paclitaxel, and rivaroxaban	NCT02921022	Active, not recruiting	NA
	Minnelide	Protein-bound paclitaxel	NCT03129139	Recruiting	Phase I
		Monotherapy	NCT04896073	Recruiting	Phase II
		Abraxane, gemcitabine	NCT05557851	Recruiting	Phase I
Focal adhesion kinase	VS-4718	Nab-paclitaxel, gemcitabine	NCT02651727	Terminated	Phase I
	Defactinib	Pembrolizumab, chemotherapy	NCT03727880	Recruiting	Phase II
		Stereotactic body radiotherapy	NCT04331041	Recruiting	Phase II
		Avutometinib, gemcitabine, and nab-paclitaxel	NCT05669482	Recruiting	Phase Ib/IIa
CXCR4	Motixafortide	Gemcitabine, nab-paclitaxel	NCT04543071	Recruiting	Phase II
Vitamin D receptor	Paricalcitol	Gemcitabine, nab-paclitaxel	NCT03520790	Active, not recruiting	Phase II
	Vitamin D	Synbiotics, omega 3	NCT05271344	Recruiting	NA
Vitamin A metabolite	ATRA	Gemcitabine, nab-paclitaxel	NCT04241276	Active, not recruiting	Phase IIb
		Nivolumab	NCT05482451	Active, not recruiting	Phase I
TGF-β signaling	PM8001	PM1021	NCT05537051	Not yet recruiting	Phase I
	Y101D	Monotherapy	NCT05028556	Not yet recruiting	Phase I

Table 2 Continued

Target	Drug	Combination therapy	Identifies	Status	Phase
IL1 signaling	Canakinumab	Tislelizumab, nab-paclitaxel, and gemcitabine	NCT05984602	Recruiting	Phase Ib
	Canakinumab	Spartalizumab, nab-paclitaxel, and gemcitabine	NCT04581343	Recruiting	Phase Ib
	Anakinra	FOLFIRINOX	NCT02021422	Unknown	Phase I
IL-6-receptor	Tocilizumab	Monotherapy	NCT06016179	Recruiting	Phase I
Metabolism	Hydroxychloroquine	Paricalcitol, gemcitabine, and nab-paclitaxel	NCT04524702	Active, not recruiting	Phase II
	U-13C-glucose	Biopsy	NCT05296421	Recruiting	NA
	AZD3965	Monotherapy	NCT01791595	Completed	Phase I
Hypoxia	Evofosfamide	Zalifrelimab, balstilimab	NCT06782555	Recruiting	Phase II
	CP-506	Carboplatin, immune checkpoint inhibitor	NCT04954599	Recruiting	Phase I/II
Leukemia inhibitory factor	AZD0171	Durvalumab, chemotherapy	NCT03490669	Active, not recruiting	Phase I
Hedgehog signaling	Vismodegib (GDC-0449)	Erlotinib hydrochloride, gemcitabine hydrochloride	NCT00878163	Active, not recruiting	Phase I
	NLM-001	Gemcitabine, nab-paclitaxel, and zalifrelimab	NCT04827953	Active, not recruiting	Phase Ib/IIa
	Taladegib	Monotherapy	NCT05199584	Active, not recruiting	Phase II

FAP, fibroblast activation protein; CAFs, cancer-associated fibroblasts; CAR-T, chimeric antigen receptor T-cell; ATRA, all-trans retinoic acid; NA, not applicable; TGF-β, transforming growth factor-β.

genomics, spatial transcriptomics, proteomics, metabolomics and organoid data, providing unprecedented insights into CAF heterogeneity, yielding dynamic biomarkers for phenotypic monitoring and facilitating data-optimized combination therapies to improve patient survival outcomes[16,17,30].

Grant support

This work was supported by the Natural Science Foundation of Hubei Province (Grant No. 2025AFB849).

Conflict of interest statement

No potential conflicts of interest are disclosed.

Author contributions

Conceived the manuscript: Jian Shen.
Collected the data: Tao Yin, Qun Wang, Lei Nie.
Prepared the figures: Jian Shen, Ruopu Wu, Lei Nie.
Wrote the paper: Jian Shen, Qun Wang.
Reviewed the manuscript: Jian Shen, Ruopu Wu, Tao Yin, Qun Wang, Lei Nie.

References

1. Garcia Garcia CJ, Huang Y, Fuentes NR, Turner MC, Monberg ME, Lin D, et al. Stromal HIF2 regulates immune suppression in the pancreatic cancer microenvironment. Gastroenterology. 2022; 162: 2018-31.
2. Quiñonero F, Mesas C, Doello K, Cabeza L, Perazzoli G, Jimenez-Luna C, et al. The challenge of drug resistance in pancreatic ductal adenocarcinoma: a current overview. Cancer Biol Med. 2019; 16: 688-99.
3. Pan H, Zhu S, Gong T, Wu D, Zhao Y, Yan J, et al. Matrix stiffness triggers chemoresistance through elevated autophagy in pancreatic ductal adenocarcinoma. Biomater Sci. 2023; 11: 7358-72.
4. Schwörer S, Cimino FV, Ros M, Tsanov KM, Ng C, Lowe SW, et al. Hypoxia potentiates the inflammatory fibroblast phenotype

promoted by pancreatic cancer cell-derived cytokines. Cancer Res. 2023; 83: 1596-610.
5. Bockorny B, Semenisty V, Macarulla T, Borazanci E, Wolpin BM, Stemmer SM, et al. BL-8040, a CXCR4 antagonist, in combination with pembrolizumab and chemotherapy for pancreatic cancer: the COMBAT trial. Nat Med. 2020; 26: 878-85.
6. Ludwig KF, Du W, Sorrelle NB, Wnuk-Lipinska K, Topalovski M, Toombs JE, et al. Small-molecule inhibition of Axl targets tumor immune suppression and enhances chemotherapy in pancreatic cancer. Cancer Res. 2018; 78: 246-55.
7. Hu S, Lu H, Xie W, Wang D, Shan Z, Xing X, et al. TDO2+ myofibroblasts mediate immune suppression in malignant transformation of squamous cell carcinoma. J Clin Invest. 2022; 132: e157649.
8. Krishnamurty AT, Shyer JA, Thai M, Gandham V, Buechler MB, Yang YA, et al. LRRC15+ myofibroblasts dictate the stromal setpoint to suppress tumour immunity. Nature. 2022; 611: 148-54.
9. Huang H, Wang Z, Zhang Y, Pradhan RN, Ganguly D, Chandra R, et al. Mesothelial cell-derived antigen-presenting cancer-associated fibroblasts induce expansion of regulatory T cells in pancreatic cancer. Cancer Cell. 2022; 40: 656-73.e7.
10. Kuzet S-E, Gaggioli C. Fibroblast activation in cancer: when seed fertilizes soil. Cell Tissue Res. 2016; 365: 607-19.
11. Chen K, Wang Q, Li M, Guo H, Liu W, Wang F, et al. Single-cell RNA-seq reveals dynamic change in tumor microenvironment during pancreatic ductal adenocarcinoma malignant progression. eBioMedicine. 2021; 66: 103315.
12. Elyada E, Bolisetty M, Laise P, Flynn WF, Courtois ET, Burkhart RA, et al. Cross-species single-cell analysis of pancreatic ductal adenocarcinoma reveals antigen-presenting cancer-associated fibroblasts. Cancer Discov. 2019; 9: 1102-23.
13. Ogawa Y, Masugi Y, Abe T, Yamazaki K, Ueno A, Fujii-Nishimura Y, et al. Three distinct stroma types in human pancreatic cancer identified by image analysis of fibroblast subpopulations and collagen. Clin Cancer Res. 2021; 27: 107-19.
14. Thorlacius-Ussing J, Jensen C, Nissen NI, Cox TR, Kalluri R, Karsdal M, et al. The collagen landscape in cancer: profiling collagens in tumors and in circulation reveals novel markers of cancer-associated fibroblast subtypes. J Pathol. 2024; 262: 22-36.
15. Biffi G, Oni TE, Spielman B, Hao Y, Elyada E, Park Y, et al. IL1-induced JAK/STAT signaling is antagonized by TGFβ to shape CAF heterogeneity in pancreatic ductal adenocarcinoma. Cancer Discov. 2019; 9: 282-301.
16. Dominguez CX, Müller S, Keerthivasan S, Koeppen H, Hung J, Gierke S, et al. Single-cell RNA sequencing reveals stromal evolution into LRRC15+ myofibroblasts as a determinant of patient response to cancer immunotherapy. Cancer Discov. 2020; 10: 232-53.
17. Wang Y, Liang Y, Xu H, Zhang X, Mao T, Cui J, et al. Single-cell analysis of pancreatic ductal adenocarcinoma identifies a novel fibroblast subtype associated with poor prognosis but better immunotherapy response. Cell Discov. 2021; 7: 36.
18. Zhu Z, Achreja A, Meurs N, Animasahun O, Owen S, Mittal A, et al. Tumour-reprogrammed stromal BCAT1 fuels branched-chain ketoacid dependency in stromal-rich PDAC tumours. Nat Metab. 2020; 2: 775-92.
19. Mizutani Y, Kobayashi H, Iida T, Asai N, Masamune A, Hara A, et al. Meflin-positive cancer-associated fibroblasts inhibit pancreatic carcinogenesis. Cancer Res. 2019; 79: 5367-81.
20. Xiao Z, Todd L, Huang L, Noguera-Ortega E, Lu Z, Huang L, et al. Desmoplastic stroma restricts T cell extravasation and mediates immune exclusion and immunosuppression in solid tumors. Nat Commun. 2023; 14: 5110.
21. Waldhauer I, Gonzalez-Nicolini V, Freimoser-Grundschober A, Nayak TK, Fahrni L, Hosse RJ, et al. Simlukafusp alfa (FAP-IL2v) immunocytokine is a versatile combination partner for cancer immunotherapy. MAbs. 2021; 13: 1913791.
22. Liu Y, Sun Y, Wang P, Li S, Dong Y, Zhou M, et al. FAP-targeted CAR-T suppresses MDSCs recruitment to improve the antitumor efficacy of claudin18.2-targeted CAR-T against pancreatic cancer. J Transl Med. 2023; 21: 255.
23. Ruixin S, Yifan L, Yansha S, Min Z, Yiwei D, Xiaoli H, et al. Dual targeting chimeric antigen receptor cells enhance antitumour activity by overcoming T cell exhaustion in pancreatic cancer. Br J Pharmacol. 2024; 181: 4628-46.
24. Wehrli M, Guinn S, Birocchi F, Kuo A, Sun Y, Larson RC, et al. Mesothelin CAR T cells secreting anti-FAP/anti-CD3 molecules efficiently target pancreatic adenocarcinoma and its stroma. Clin Cancer Res. 2024; 30: 1859-77.
25. Duperret EK, Trautz A, Ammons D, Perales-Puchalt A, Wise MC, Yan J, et al. Alteration of the tumor stroma using a consensus DNA vaccine targeting fibroblast activation protein (FAP) synergizes with antitumor vaccine therapy in mice. Clin Cancer Res. 2018; 24: 1190-201.
26. Karamitopoulou E, Wenning AS, Acharjee A, Zlobec I, Aeschbacher P, Perren A, et al. Spatially restricted tumour-associated and host-associated immune drivers correlate with the recurrence sites of pancreatic cancer. Gut. 2023; 72: 1523-33.
27. Özdemir BC, Pentcheva-Hoang T, Carstens JL, Zheng X, Wu C-C, Simpson TR, et al. Depletion of carcinoma-associated fibroblasts and fibrosis induces immunosuppression and accelerates pancreas cancer with reduced survival. Cancer Cell. 2014; 25: 719-34.
28. Lee YE, Go G-Y, Koh E-Y, Yoon H-N, Seo M, Hong S-M, et al. Synergistic therapeutic combination with a CAF inhibitor enhances CAR-NK-mediated cytotoxicity via reduction of CAF-released IL-6. J Immunother Cancer. 2023; 11: e006130.
29. Amit U, Uslu U, Verginadis II, Kim MM, Motlagh SAO, Diffenderfer ES, et al. Proton radiation boosts the efficacy of mesothelin-targeting chimeric antigen receptor T cell therapy in pancreatic cancer. Proc Natl Acad Sci U S A. 2024; 121: e2403002121.
30. Zhang H, Zhu H, Feng J, Zhang Z, Zhang S, Wang Z, et al. Reprogramming of activated pancreatic stellate cells via mechanical modulation of transmembrane force-sensitive N-cadherin receptor. J Mol Biol. 2023; 435: 167819.

31. Kocher HM, Basu B, Froeling FEM, Sarker D, Slater S, Carlin D, et al. Phase I clinical trial repurposing all-trans retinoic acid as a stromal targeting agent for pancreatic cancer. Nat Commun. 2020; 11: 4841.
32. Cui J, Gong M, He Y, Li Q, He T, Bi Y. All-trans retinoic acid inhibits proliferation, migration, invasion and induces differentiation of hepa1-6 cells through reversing EMT in vitro. Int J Oncol. 2016; 48: 349-57.
33. Gorchs L, Ahmed S, Mayer C, Knauf A, Fernández Moro C, Svensson M, et al. The vitamin D analogue calcipotriol promotes an anti-tumorigenic phenotype of human pancreatic CAFs but reduces T cell mediated immunity. Sci Rep. 2020; 10: 17444.
34. Mukai Y, Yamada D, Eguchi H, Iwagami Y, Asaoka T, Noda T, et al. Vitamin D supplementation is a promising therapy for pancreatic ductal adenocarcinoma in conjunction with current chemoradiation therapy. Ann Surg Oncol. 2018; 25: 1868-79.
35. Evans TRJ, Colston KW, Lofts FJ, Cunningham D, Anthoney DA, Gogas H, et al. A phase II trial of the vitamin D analogue seocalcitol (EB1089) in patients with inoperable pancreatic cancer. Br J Cancer. 2002; 86: 680-5.
36. Borazanci E, Jameson G, Korn R, Caldwell L, Ansaldo K, Hendrickson K, et al. A phase II pilot trial of nivolumab (N) + albumin bound paclitaxel (AP) + paricalcitol (P) + cisplatin (C) + gemcitabine (G) (NAPPCG) in patients with previously untreated metastatic pancreatic ductal adenocarcinoma (PDAC). Cancer Res. 2019; 79: CT152.
37. Mizutani Y, Iida T, Ohno E, Ishikawa T, Kinoshita F, Kuwatsuka Y, et al. Safety and efficacy of MIKE-1 in patients with advanced pancreatic cancer: a study protocol for an open-label phase I/II investigator-initiated clinical trial based on a drug repositioning approach that reprograms the tumour stroma. BMC Cancer. 2022; 22: 205.
38. Zhang Y, Ware MB, Zaidi MY, Ruggieri AN, Olson BM, Komar H, et al. Heat shock protein-90 inhibition alters activation of pancreatic stellate cells and enhances the efficacy of PD-1 blockade in pancreatic cancer. Mol Cancer Ther. 2021; 20: 150-60.
39. Chen Y, Kim J, Yang S, Wang H, Wu C-J, Sugimoto H, et al. Type I collagen deletion in αSMA^+ myofibroblasts augments immune suppression and accelerates progression of pancreatic cancer. Cancer Cell. 2021; 39: 548-65.e6.
40. Elahi-Gedwillo KY, Carlson M, Zettervall J, Provenzano PP. Antifibrotic therapy disrupts stromal barriers and modulates the immune landscape in pancreatic ductal adenocarcinoma. Cancer Res. 2019; 79: 372-86.
41. Hingorani SR, Zheng L, Bullock AJ, Seery TE, Harris WP, Sigal DS, et al. HALO 202: randomized phase ii study of PEGPH20 plus nab-paclitaxel/gemcitabine versus nab-paclitaxel/gemcitabine in patients with untreated, metastatic pancreatic ductal adenocarcinoma. J Clin Oncol. 2018; 36: 359-66.
42. Van Cutsem E, Tempero MA, Sigal D, Oh D-Y, Fazio N, Macarulla T, et al. Randomized phase III trial of pegvorhyaluronidase alfa with nab-paclitaxel plus gemcitabine for patients with hyaluronan-high metastatic pancreatic adenocarcinoma. J Clin Oncol. 2020; 38: 3185-94.
43. Modi S, Giri B, Gupta VK, Lavania S, Sethi V, Sharma NS, et al. Minnelide synergizes with conventional chemotherapy by targeting both cancer and associated stroma components in pancreatic cancer. Cancer Lett. 2022; 537: 215591.
44. Boucher Y, Posada JM, Subudhi S, Kumar AS, Rosario SR, Gu L, et al. Addition of losartan to FOLFIRINOX and chemoradiation reduces immunosuppression-associated genes, Tregs, and FOXP3+ cancer cells in locally advanced pancreatic cancer. Clin Cancer Res. 2023; 29: 1605-19.
45. Lander VE, Belle JI, Kingston NL, Herndon JM, Hogg GD, Liu X, et al. Stromal reprogramming by FAK inhibition overcomes radiation resistance to allow for immune priming and response to checkpoint blockade. Cancer Discov. 2022; 12: 2774-99.
46. Lim K-H, Spencer KR, Safyan RA, Picozzi VJ, Varghese AM, Siolas D, et al. Avutometinib/defactinib and gemcitabine/nab-paclitaxel combination in first-line metastatic pancreatic ductal adenocarcinoma: initial safety and efficacy of phase 1b/2 study (RAMP 205). J Clin Oncol. 2024; 42: 4140.
47. Wei Y, Song S, Duan N, Wang F, Wang Y, Yang Y, et al. MT1-MMP-activated liposomes to improve tumor blood perfusion and drug delivery for enhanced pancreatic cancer therapy. Adv Sci (Weinh). 2020; 7: 1902746.
48. Van Doren SR. MMP-7 marks severe pancreatic cancer and alters tumor cell signaling by proteolytic release of ectodomains. Biochem Soc Trans. 2022; 50: 839-51.
49. Bramhall SR, Schulz J, Nemunaitis J, Brown PD, Baillet M, Buckels JAC. A double-blind placebo-controlled, randomised study comparing gemcitabine and marimastat with gemcitabine and placebo as first line therapy in patients with advanced pancreatic cancer. Br J Cancer. 2002; 87: 161-7.
50. Moore MJ, Hamm J, Dancey J, Eisenberg PD, Dagenais M, Fields A, et al. Comparison of gemcitabine versus the matrix metalloproteinase inhibitor BAY 12-9566 in patients with advanced or metastatic adenocarcinoma of the pancreas: a phase III trial of the National Cancer Institute of Canada Clinical Trials Group. J Clin Oncol. 2003; 21: 3296-302.
51. Ji T, Lang J, Wang J, Cai R, Zhang Y, Qi F, et al. Designing liposomes to suppress extracellular matrix expression to enhance drug penetration and pancreatic tumor therapy. ACS Nano. 2017; 11: 8668-78.
52. Peran I, Dakshanamurthy S, McCoy MD, Mavropoulos A, Allo B, Sebastian A, et al. Cadherin 11 promotes immunosuppression and extracellular matrix deposition to support growth of pancreatic tumors and resistance to gemcitabine in mice. Gastroenterology. 2021; 160: 1359-72.e13.
53. Zhang D, Li L, Jiang H, Li Q, Wang-Gillam A, Yu J, et al. Tumor-stroma IL1β-IRAK4 feedforward circuitry drives tumor fibrosis, chemoresistance, and poor prognosis in pancreatic cancer. Cancer Res. 2018; 78: 1700-12.
54. Somani VK, Zhang D, Dodhiawala PB, Lander VE, Liu X, Kang L-I, et al. IRAK4 signaling drives resistance to checkpoint immunotherapy in pancreatic ductal adenocarcinoma. Gastroenterology. 2022; 162: 2047-62.

55. Huang H, Zhang Y, Gallegos V, Sorrelle N, Zaid MM, Toombs J, et al. Targeting TGFβR2-mutant tumors exposes vulnerabilities to stromal TGFβ blockade in pancreatic cancer. EMBO Mol Med. 2019; 11: e10515.
56. Gu J, Li X, Zhao L, Yang Y, Xue C, Gao Y, et al. The role of PKM2 nuclear translocation in the constant activation of the NF-κB signaling pathway in cancer-associated fibroblasts. Cell Death Dis. 2021; 12: 291.
57. Garg B, Giri B, Modi S, Sethi V, Castro I, Umland O, et al. NFκB in pancreatic stellate cells reduces infiltration of tumors by cytotoxic T cells and killing of cancer cells, via up-regulation of CXCL12. Gastroenterology. 2018; 155: 880-91.e8.
58. Shi Y, Gao W, Lytle NK, Huang P, Yuan X, Dann AM, et al. Targeting LIF-mediated paracrine interaction for pancreatic cancer therapy and monitoring. Nature. 2019; 569: 131-5.
59. Borazanci E, Schram AM, Garralda E, Brana I, Vieito Villar M, Spreafico A, et al. Phase I, first-in-human study of MSC-1 (AZD0171), a humanized anti-leukemia inhibitory factor monoclonal antibody, for advanced solid tumors. ESMO Open. 2022; 7: 100530.
60. Hurwitz H, Van Cutsem E, Bendell J, Hidalgo M, Li C-P, Salvo MG, et al. Ruxolitinib + capecitabine in advanced/metastatic pancreatic cancer after disease progression/intolerance to first-line therapy: JANUS 1 and 2 randomized phase III studies. Invest New Drugs. 2018; 36: 683-95.
61. Long KB, Tooker G, Tooker E, Luque SL, Lee JW, Pan X, et al. IL6 receptor blockade enhances chemotherapy efficacy in pancreatic ductal adenocarcinoma. Mol Cancer Ther. 2017; 16: 1898-908.
62. Siddiqui I, Erreni M, Kamal MA, Porta C, Marchesi F, Pesce S, et al. Differential role of Interleukin-1 and Interleukin-6 in K-Ras-driven pancreatic carcinoma undergoing mesenchymal transition. Oncoimmunology. 2017; 7: e1388485.
63. Pozios I, Seel NN, Hering NA, Hartmann L, Liu V, Camaj P, et al. Raloxifene inhibits pancreatic adenocarcinoma growth by interfering with ERβ and IL-6/gp130/STAT3 signaling. Cell Oncol (Dordr). 2021; 44: 167-77.
64. Mace TA, Shakya R, Pitarresi JR, Swanson B, McQuinn CW, Loftus S, et al. IL-6 and PD-L1 antibody blockade combination therapy reduces tumour progression in murine models of pancreatic cancer. Gut. 2018; 67: 320-32.
65. Datta J, Dai X, Bianchi A, De Castro Silva I, Mehra S, Garrido VT, et al. Combined MEK and STAT3 inhibition uncovers stromal plasticity by enriching for cancer-associated fibroblasts with mesenchymal stem cell-like features to overcome immunotherapy resistance in pancreatic cancer. Gastroenterology. 2022; 163: 1593-612.
66. Melisi D, Oh D-Y, Hollebecque A, Calvo E, Varghese A, Borazanci E, et al. Safety and activity of the TGFβ receptor I kinase inhibitor galunisertib plus the anti-PD-L1 antibody durvalumab in metastatic pancreatic cancer. J Immunother Cancer. 2021; 9: e002068.
67. Bockorny B, Macarulla T, Semenisty V, Borazanci E, Feliu J, Ponz-Sarvise M, et al. Motixafortide and pembrolizumab combined to nanoliposomal irinotecan, fluorouracil, and folinic acid in metastatic pancreatic cancer: the COMBAT/KEYNOTE-202 trial. Clin Cancer Res. 2021; 27: 5020-7.
68. Suarez-Carmona M, Williams A, Schreiber J, Hohmann N, Pruefer U, Krauss J, et al. Combined inhibition of CXCL12 and PD-1 in MSS colorectal and pancreatic cancer: modulation of the microenvironment and clinical effects. J Immunother Cancer. 2021; 9: e002505.
69. Catenacci DVT, Junttila MR, Karrison T, Bahary N, Horiba MN, Nattam SR, et al. Randomized phase Ib/II study of gemcitabine plus placebo or vismodegib, a hedgehog pathway inhibitor, in patients with metastatic pancreatic cancer. J Clin Oncol. 2015; 33: 4284-92.
70. Oyama Y, Onishi H, Koga S, Murahashi M, Ichimiya S, Nakayama K, et al. Patched 1-interacting peptide represses fibrosis in pancreatic cancer to augment the effectiveness of immunotherapy. J Immunother. 2020; 43: 121-33.
71. Lee JJ, Perera RM, Wang H, Wu D-C, Liu XS, Han S, et al. Stromal response to Hedgehog signaling restrains pancreatic cancer progression. Proc Natl Acad Sci U S A. 2014; 111: E3091-100.
72. Rucki AA, Xiao Q, Muth S, Chen J, Che X, Kleponis J, et al. Dual inhibition of hedgehog and c-Met pathways for pancreatic cancer treatment. Mol Cancer Ther. 2017; 16: 2399-409.
73. Tape CJ, Ling S, Dimitriadi M, McMahon KM, Worboys JD, Leong HS, et al. Oncogenic KRAS regulates tumor cell signaling via stromal reciprocation. Cell. 2016; 165: 910-20.
74. Zhang Y, Arner EN, Rizvi A, Toombs JE, Huang H, Warner SL, et al. AXL inhibitor TP-0903 reduces metastasis and therapy resistance in pancreatic cancer. Mol Cancer Ther. 2022; 21: 38-47.
75. Abdel-Wahab R, Varadhachary GR, Bhosale PR, Wang X, Fogelman DR, Shroff RT, et al. Randomized, phase I/II study of gemcitabine plus IGF-1R antagonist (MK-0646) versus gemcitabine plus erlotinib with and without MK-0646 for advanced pancreatic adenocarcinoma. J Hematol Oncol. 2018; 11: 71.
76. Fuchs CS, Azevedo S, Okusaka T, Van Laethem J-L, Lipton LR, Riess H, et al. A phase 3 randomized, double-blind, placebo-controlled trial of ganitumab or placebo in combination with gemcitabine as first-line therapy for metastatic adenocarcinoma of the pancreas: the GAMMA trial. Ann Oncol. 2015; 26: 921-7.
77. Kundranda M, Gracian AC, Zafar SF, Meiri E, Bendell J, Algül H, et al. Randomized, double-blind, placebo-controlled phase II study of istiratumab (MM-141) plus nab-paclitaxel and gemcitabine versus nab-paclitaxel and gemcitabine in front-line metastatic pancreatic cancer (CARRIE). Ann Oncol. 2020; 31: 79-87.
78. Philip PA, Goldman B, Ramanathan RK, Lenz H-J, Lowy AM, Whitehead RP, et al. Dual blockade of epidermal growth factor receptor and insulin-like growth factor receptor-1 signaling in metastatic pancreatic cancer: phase Ib and randomized phase II trial of gemcitabine, erlotinib, and cixutumumab versus gemcitabine plus erlotinib (SWOG S0727). Cancer. 2014; 120: 2980-5.
79. Pothula SP, Xu Z, Goldstein D, Pirola RC, Wilson JS, Apte MV. Targeting HGF/c-MET axis in pancreatic cancer. Int J Mol Sci. 2020; 21: 9170.
80. Pothula SP, Xu Z, Goldstein D, Biankin AV, Pirola RC, Wilson JS, et al. Hepatocyte growth factor inhibition: a novel therapeutic approach in pancreatic cancer. Br J Cancer. 2016; 114: 269-80.

81. Takiguchi S, Inoue K, Matsusue K, Furukawa M, Teramoto N, Iguchi H. Crizotinib, a MET inhibitor, prevents peritoneal dissemination in pancreatic cancer. Int J Oncol. 2017; 51: 184-92.
82. Rosen LS, Goldman JW, Algazi AP, Turner PK, Moser B, Hu T, et al. A first-in-human phase I study of a bivalent MET antibody, emibetuzumab (LY2875358), as monotherapy and in combination with erlotinib in advanced cancer. Clin Cancer Res. 2017; 23: 1910-9.
83. Xu Z, Pang TCY, Liu AC, Pothula SP, Mekapogu AR, Perera CJ, et al. Targeting the HGF/c-MET pathway in advanced pancreatic cancer: a key element of treatment that limits primary tumour growth and eliminates metastasis. Br J Cancer. 2020; 122: 1486-95.
84. Zhen DB, Griffith KA, Ruch JM, Camphausen K, Savage JE, Kim EJ, et al. A phase I trial of cabozantinib and gemcitabine in advanced pancreatic cancer. Invest New Drugs. 2016; 34: 733-9.
85. Mekapogu AR, Xu Z, Pothula S, Perera C, Pang T, Hosen SMZ, et al. HGF/c-Met pathway inhibition combined with chemotherapy increases cytotoxic T-cell infiltration and inhibits pancreatic tumour growth and metastasis. Cancer Lett. 2023; 568: 216286.
86. Patel MB, Pothula SP, Xu Z, Lee AK, Goldstein D, Pirola RC, et al. The role of the hepatocyte growth factor/c-MET pathway in pancreatic stellate cell-endothelial cell interactions: antiangiogenic implications in pancreatic cancer. Carcinogenesis. 2014; 35: 1891-900.
87. Sano M, Ijichi H, Takahashi R, Miyabayashi K, Fujiwara H, Yamada T, et al. Blocking CXCLs-CXCR2 axis in tumor-stromal interactions contributes to survival in a mouse model of pancreatic ductal adenocarcinoma through reduced cell invasion/migration and a shift of immune-inflammatory microenvironment. Oncogenesis. 2019; 8: 8.
88. Sun X, He X, Zhang Y, Hosaka K, Andersson P, Wu J, et al. Inflammatory cell-derived CXCL3 promotes pancreatic cancer metastasis through a novel myofibroblast-hijacked cancer escape mechanism. Gut. 2022; 71: 129-47.
89. Prajapati DR, Molczyk C, Purohit A, Saxena S, Sturgeon R, Dave BJ, et al. Small molecule antagonist of CXCR2 and CXCR1 inhibits tumor growth, angiogenesis, and metastasis in pancreatic cancer. Cancer Lett. 2023; 563: 216185.
90. Chen X, An Y, Zhang Y, Xu D, Chen T, Yang Y, et al. CCL26 is upregulated by nab-paclitaxel in pancreatic cancer-associated fibroblasts and promotes PDAC invasiveness through activation of the PI3K/AKT/mTOR pathway. Acta Biochim Biophys Sin (Shanghai). 2021; 53: 612-9.
91. Nywening TM, Wang-Gillam A, Sanford DE, Belt BA, Panni RZ, Cusworth BM, et al. Targeting tumour-associated macrophages with CCR2 inhibition in combination with FOLFIRINOX in patients with borderline resectable and locally advanced pancreatic cancer: a single-centre, open-label, dose-finding, non-randomised, phase 1b trial. Lancet Oncol. 2016; 17: 651-62.
92. Noel M, O'Reilly EM, Wolpin BM, Ryan DP, Bullock AJ, Britten CD, et al. Phase 1b study of a small molecule antagonist of human chemokine (C-C motif) receptor 2 (PF-04136309) in combination with nab-paclitaxel/gemcitabine in first-line treatment of metastatic pancreatic ductal adenocarcinoma. Invest New Drugs. 2020; 38: 800-11.
93. Liang L, Li W, Li X, Jin X, Liao Q, Li Y, et al. 'Reverse Warburg effect' of cancer-associated fibroblasts (Review). Int J Oncol. 2022; 60: 67.
94. Pethő Z, Najder K, Beel S, Fels B, Neumann I, Schimmelpfennig S, et al. Acid-base homeostasis orchestrated by NHE1 defines the pancreatic stellate cell phenotype in pancreatic cancer. JCI Insight. 2023; 8: e170928.
95. Shan T, Chen S, Chen X, Lin WR, Li W, Ma J, et al. Cancer-associated fibroblasts enhance pancreatic cancer cell invasion by remodeling the metabolic conversion mechanism. Oncol Rep. 2017; 37: 1971-9.
96. Xie Y, Zhou T, Li X, Zhao K, Bai W, Hou X, et al. Targeting ESE3/EHF with nifurtimox inhibits CXCR2+ neutrophil infiltration and overcomes pancreatic cancer resistance to chemotherapy and immunotherapy. Gastroenterology. 2024; 167: 281-97.
97. Kitamura F, Semba T, Yasuda-Yoshihara N, Yamada K, Nishimura A, Yamasaki J, et al. Cancer-associated fibroblasts reuse cancer-derived lactate to maintain a fibrotic and immunosuppressive microenvironment in pancreatic cancer. JCI Insight. 2023; 8: e163022.
98. Jena BC, Das CK, Banerjee I, Bharadwaj D, Majumder R, Das S, et al. TGF-β1 induced autophagy in cancer associated fibroblasts during hypoxia contributes EMT and glycolysis via MCT4 upregulation. Exp Cell Res. 2022; 417: 113195.
99. Curtis NJ, Mooney L, Hopcroft L, Michopoulos F, Whalley N, Zhong H, et al. Pre-clinical pharmacology of AZD3965, a selective inhibitor of MCT1: DLBCL, NHL and Burkitt's lymphoma anti-tumor activity. Oncotarget. 2017; 8: 69219-36.
100. Halford S, Veal GJ, Wedge SR, Payne GS, Bacon CM, Sloan P, et al. A phase I dose-escalation study of AZD3965, an oral monocarboxylate transporter 1 inhibitor, in patients with advanced cancer. Clin Cancer Res. 2023; 29: 1429-39.
101. Hu X, Peng X, Zhang Y, Fan S, Liu X, Song Y, et al. Shikonin reverses cancer-associated fibroblast-induced gemcitabine resistance in pancreatic cancer cells by suppressing monocarboxylate transporter 4-mediated reverse Warburg effect. Phytomedicine. 2024; 123: 155214.
102. Benjamin D, Robay D, Hindupur SK, Pohlmann J, Colombi M, El-Shemerly MY, et al. Dual inhibition of the lactate transporters MCT1 and MCT4 is synthetic lethal with metformin due to NAD+ depletion in cancer cells. Cell Rep. 2018; 25: 3047-58.e4.
103. Hou X, Zhang J, Wang Y, Xiong W, Mi J. TGFBR-IDH1-Cav1 axis promotes TGF-β signalling in cancer-associated fibroblast. Oncotarget. 2017; 8: 83962-74.
104. Zarei M, Hajihassani O, Hue JJ, Loftus AW, Graor HJ, Nakazzi F, et al. IDH1 inhibition potentiates chemotherapy efficacy in pancreatic cancer. Cancer Res. 2024; 84: 3072-85.
105. Yuan M, Tu B, Li H, Pang H, Zhang N, Fan M, et al. Cancer-associated fibroblasts employ NUFIP1-dependent autophagy to secrete nucleosides and support pancreatic tumor growth. Nat Cancer. 2022; 3: 945-60.

106. Francescone R, Barbosa Vendramini-Costa D, Franco-Barraza J, Wagner J, Muir A, Lau AN, et al. Netrin G1 promotes pancreatic tumorigenesis through cancer-associated fibroblast-driven nutritional support and immunosuppression. Cancer Discov. 2021; 11: 446-79.
107. Bai J, Liu T, Tu B, Yuan M, Shu Z, Fan M, et al. Autophagy loss impedes cancer-associated fibroblast activation via downregulating proline biosynthesis. Autophagy. 2023; 19: 632-43.
108. Parker SJ, Amendola CR, Hollinshead KER, Yu Q, Yamamoto K, Encarnación-Rosado J, et al. Selective alanine transporter utilization creates a targetable metabolic niche in pancreatic cancer. Cancer Discov. 2020; 10: 1018-37.
109. Niu N, Shen X, Wang Z, Chen Y, Weng Y, Yu F, et al. Tumor cell-intrinsic epigenetic dysregulation shapes cancer-associated fibroblasts heterogeneity to metabolically support pancreatic cancer. Cancer Cell. 2024; 42: 869-84.e9.
110. Mhaidly R, Mechta-Grigoriou F. Fibroblast heterogeneity in tumor micro-environment: role in immunosuppression and new therapies. Semin Immunol. 2020; 48: 101417.
111. Li W, Cao L, Chen X, Lei J, Ma Q. Resveratrol inhibits hypoxia-driven ROS-induced invasive and migratory ability of pancreatic cancer cells via suppression of the Hedgehog signaling pathway. Oncol Rep. 2016; 35: 1718-26.
112. Becker LM, O'Connell JT, Vo AP, Cain MP, Tampe D, Bizarro L, et al. Epigenetic reprogramming of cancer-associated fibroblasts deregulates glucose metabolism and facilitates progression of breast cancer. Cell Rep. 2020; 31: 107701.
113. Deng K, Zou F, Xu J, Xu D, Luo Z. Cancer-associated fibroblasts promote stemness maintenance and gemcitabine resistance via HIF-1α/miR-21 axis under hypoxic conditions in pancreatic cancer. Mol Carcinog. 2024; 63: 524-37.
114. Kishimoto S, Brender JR, Chandramouli GVR, Saida Y, Yamamoto K, Mitchell JB, et al. Hypoxia-activated prodrug evofosfamide treatment in pancreatic ductal adenocarcinoma xenografts alters the tumor redox status to potentiate radiotherapy. Antioxid Redox Signal. 2021; 35: 904-15.
115. Borad MJ, Reddy SG, Bahary N, Uronis HE, Sigal D, Cohn AL, et al. Randomized phase II trial of gemcitabine plus TH-302 versus gemcitabine in patients with advanced pancreatic cancer. J Clin Oncol. 2015; 33: 1475-81.
116. Grande E, Rodriguez-Antona C, López C, Alonso-Gordoa T, Benavent M, Capdevila J, et al. Sunitinib and evofosfamide (TH-302) in systemic treatment-naïve patients with grade 1/2 metastatic pancreatic neuroendocrine tumors: the GETNE-1408 trial. Oncologist. 2021; 26: 941-9.
117. Ma WW, Xie H, Fetterly G, Pitzonka L, Whitworth A, LeVea C, et al. A phase Ib study of the FGFR/VEGFR inhibitor dovitinib with gemcitabine and capecitabine in advanced solid tumor and pancreatic cancer patients. Am J Clin Oncol. 2019; 42: 184-9.
118. Yamaue H, Tsunoda T, Tani M, Miyazawa M, Yamao K, Mizuno N, et al. Randomized phase II/III clinical trial of elpamotide for patients with advanced pancreatic cancer: PEGASUS-PC study. Cancer Sci. 2015; 106: 883-90.
119. Liu Y, Zhang X, Gu W, Su H, Wang X, Wang X, et al. Unlocking the crucial role of cancer-associated fibroblasts in tumor metastasis: mechanisms and therapeutic prospects. J Adv Res. 2025; 71: 399-413.

Cite this article as: Shen J, Wu R, Yin T, Wang Q, Nie L. Harnessing the power of cancer-associated fibroblasts to revolutionize pancreatic cancer treatment. Cancer Biol Med. 2025; 22: 1473-1492. doi: 10.20892/j.issn.2095-3941.2025.0288