Journal of Hepatocellular Carcinoma

Dovepress
Taylor & Francis Group

Open Access Full Text Article

REVIEW

Cancer-Associated Fibroblasts in the Treatment of Intrahepatic Cholangiocarcinoma: Present and Prospects

Yimeng Yuan[1,*], Ruoyu Zhang[1,*], Chengkang Qu[1], Ning Huang[1], Liming Wang[1], Mei Liu[2]

[1]Department of Hepatobiliary Surgery, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, People's Republic of China; [2]Laboratory of Cell and Molecular Biology & State Key Laboratory of Molecular Oncology, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, People's Republic of China

*These authors contributed equally to this work

Correspondence: Mei Liu, Laboratory of Cell and Molecular Biology & State Key Laboratory of Molecular Oncology, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, People's Republic of China, Tel +86-1087788487, Email liumei@cicams.ac.cn; Liming Wang, Department of Hepatobiliary Surgery, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, People's Republic of China, Tel +86-13161361180, Email stewen_wang@sina.com

Abstract: Intrahepatic cholangiocarcinoma (ICC) is a rare, highly malignant, and heterogeneous group of primary hepatic adenocarcinomas that differs distinctly from conventional hepatocellular carcinoma. A specific cell population plays a crucial role in ICC named cancer-associated fibroblasts (CAFs). CAFs are involved in the connective tissue proliferative response in ICC, and this response manifests as a dense, fibrocollagen-rich tumor stroma. Thus, although chemotherapy and radiotherapy are the primary approaches to improve survival rates in patients with ICC, the presence of CAFs still render many patients refractory to these therapies. In this article, we explored the complex disease process of ICC in depth, reviewed the origin, heterogeneity, and function of CAFs, and focused on how CAFs subpopulations could be used as biomarkers and contribute to ICC treatment resistance. We also described current breakthroughs in targeting CAFs to overcome cancer treatment resistance and discussed emerging targeted therapies for CAFs. This article aims to provide a comprehensive overview of the latest advances and breakthrough directions in ICC treatment, hoping to offer new insights for future research and clinical practice.

Keywords: cancer-associated fibroblasts, cancer therapy, drug resistance, intrahepatic cholangiocarcinoma, resistance mechanisms, tumor microenvironment

Introduction

Intrahepatic cholangiocarcinoma (ICC) is a rare but highly invasive tumor, accounting for approximately 10~20% of all liver malignancies and 1%~3% of all gastrointestinal malignancies.[1,2] It originates from the epithelium of the secondary bile ducts and their branches and is an adenocarcinoma rich in fibrotic stroma. A key constituent of this stroma is cancer-associated fibroblasts (CAFs). They are the most representative stromal cell type that modulates the formation and functional properties of the fibrotic microenvironment in ICC.[3] ICC's etiology is complex and is generally believed to result from the combined effects of multiple factors especially chronic inflammation. These include chronic hepatitis and cirrhosis, chronic inflammatory diseases of the biliary tract, parasitic infections, exposure to chemicals and toxins, congenital biliary tract diseases (particularly Caroli's disease), diabetes, and certain genetic disorders.[2] Early symptoms of ICC are not obvious, but as the disease progresses, patients may experience abdominal discomfort, jaundice, hepatomegaly, or abdominal masses. Due to its high invasiveness and metastatic potential, most patients are diagnosed at a locally advanced or metastatic stage, which undoubtedly poses a significant challenge to the treatment of ICC.[4] Traditional surgical procedures, chemotherapy, and immune checkpoint inhibitors have demonstrated relatively

https://doi.org/10.2147/JHC.S581943
Received: 17 November 2025
Accepted: 1 March 2026
Published: 23 March 2026

promising efficacy in the treatment of many solid tumors, offering hope for survival to ICC patients. However, even for patients with resectable ICC, the 5-year overall survival rate after liver resection is still less than 40%.[5,6] For patients who are not eligible for surgery, especially those with locally advanced or metastatic cholangiocarcinoma, gemcitabine combined with cisplatin is the standard first-line chemotherapy regimen. However, the median overall survival in ICC patients remains less than 1 year.[7,8] In the era of immunochemotherapy and precision targeted therapy, the immunochemotherapy regimen from the TOPAZ-1 study improves survival but offers limited benefit.[9] This suboptimal treatment outcome is largely related to the issue of drug resistance in ICC. The current situation of drug resistance in ICC is extremely severe, with multiple mechanisms of resistance coexisting, making treatment even more difficult. CAFs have been proven to play a role in mediating treatment resistance across other cancer types.[10] Therefore, we hypothesize that the presence of CAFs is associated with treatment resistance in ICC.

Unlike traditional hepatocellular carcinoma (HCC), one of the main characteristics of ICC is a complex, dynamic, and evolving connective tissue proliferative response.[11] CAFs are the most representative type of stromal cells that support the above reactions.[12] Among these cells, the enrichment of α-smooth muscle actin-positive (α-SMA$^+$) CAFs serves as a hallmark histological feature of ICC,[13] and is accompanied by the deposition of dense extracellular matrix (ECM) proteins, including collagen, hyaluronic acid (HA), and other proteoglycans.[14] This reaction forms a tough but avascular scaffold composed of a dense fibrous collagen matrix, which occupies most of the tumor tissue.[15] The dense desmoplastic stroma within ICC is the fundamental cause of its targetoid or delayed enhancement pattern on CT/MRI imaging, a feature distinct from the rapid washout pattern of HCC. And also constitutes one of the core challenges in the current radiological differential diagnosis of ICC.[16] Meanwhile, this connective tissue proliferative reaction is associated with poor clinical outcomes in ICC patients. However, due to the heterogeneous phenotypic and functional properties of CAFs, their role in tumor biology especially ICC fields is complex and not yet fully understood. Although abundant infiltration of CAFs is a characteristic feature of ICC at the mechanistic level, highly specific and well-established diagnostic markers for CAFs are still lacking in clinical practice, with no ideal indicator comparable to alpha-fetoprotein for HCC.[17]

Therefore, this article provides a detailed review of the diverse drug resistance mechanisms mediated by CAFs in ICC. We also aim to explore promising CAF-related therapeutic targets, with the expectation that these insights will offer scientific guidance for ICC treatment and ultimately improve patient outcomes and quality of life.

Origin and Heterogeneity of CAFs in ICC

CAFs are a distinct cell population in the tumor microenvironment (TME) of ICC patients, with α-SMA$^+$ myofibroblast-like cells being particularly prominent in the unique fibrotic stroma of ICC patients.[18] Unlike quiescent fibroblasts in normal tissues, CAFs are spindle-shaped fibroblasts with abnormally activated functions in solid tumors, and exhibiting significantly increased expression of α-SMA and type I collagen (Col I).[8,17] So CAFs are a major source of collagen production. In tumor tissues, CAFs account for nearly 70% of the cellular population and can promote tumor progression in multiple ways, including inducing tumor cell resistance.[19]

Origin of CAFs

CAFs may originate from various cell types as shown in Figure 1: (1) Activated hepatic stellate cells (HSCs) are the primary source of myofibroblasts in ICC.[17] Under the induction of this microRNA-21 by HCC tumor cells, HSCs can differentiate into α-SMA$^+$ CAFs and fibroblast activation protein -positive (FAP$^+$) CAFs. These activated CAFs express high levels of vascular endothelial growth factor (VEGF), which further promotes the progression of tumor cells.[20] (2) Resident fibroblasts in the tumor stroma; Tumor cells secrete various cytokines, such as transforming growth factor-β (TGF-β) and platelet-derived growth factor (PDGF). These cytokines can induce resident fibroblasts in the tumor stroma to differentiate into CAFs.[21] (3) The transformation of epithelial cells into mesenchymal cells, occurring under specific physiological and pathological conditions, is defined as epithelial-to-mesenchymal transition (EMT).[22] During this EMT process, epithelial cells lose their epithelial ECM characteristics, such as polarity, intercellular tight junctions, and adherens junctions. In addition, epithelial cells acquire mesenchymal cell characteristics, such as enhanced migration and invasion abilities, anti-apoptotic ability, and the ability to produce ECM components.[23] Some CAFs have been shown to potentially differentiate from epithelial cells through EMT in various cancers such as breast cancer, kidney cancer, lung

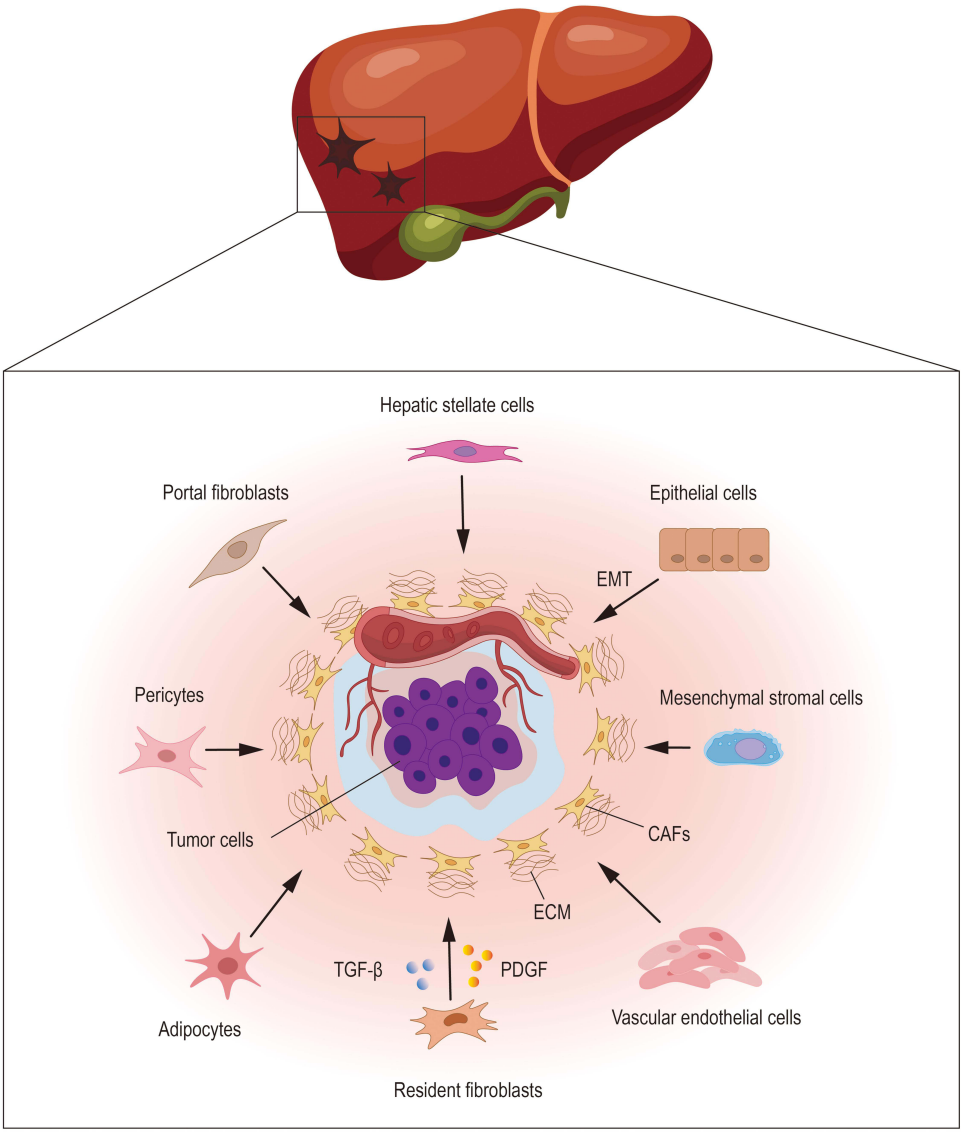

Figure 1 The originations of CAFs. CAFs originate from multiple cell types: Hepatic stellate cells, portal fibroblasts, pericytes, adipocytes can directly differentiate into CAFs. Resident fibroblasts transform into CAFs under cytokines (TGF-β, PDGF) stimulation. Epithelial cells undergo EMT to become CAFs, and mesenchymal stromal cells, vascular endothelial cells also contribute to CAF formation, with ECM involved in the microenvironment.

Abbreviations: CAFs, Cancer-Associated Fibroblasts; ECM, Extracellular Matrix; EMT, Epithelial to Mesenchymal Transition; HSCs, Hepatic Stellate Cells; PDGF, Platelet-Derived Growth Factor; PFs, Portal Fibroblasts; TGF-β, Transforming Growth Factor-β.

cancer, and liver cancer.[24,25] (4) Portal fibroblasts (PFs); Located in the periportal area, PFs play a role in maintaining the integrity of both bile duct branches and portal vein ducts.[26] Itou et al characterized CAFs in metastatic lymph nodes and confirmed that PFs are the source of CAFs in the primary site of ICC and this source is associated with the positive expression of PDGF Receptor-β (PDGFR-β), fibronectin 2, and thymocyte antigen-1.[27] (5) Pericytes, which surround endothelial cells in capillaries and veins throughout the body, can be reprogrammed into CAFs in a PDGF-dependent manner.[28] (6) CAFs can also be derived from bone marrow-derived mesenchymal stem cells (BM-MSCs); BM-MSCs are a population of adult stem cells present in the bone marrow stroma. BM-MSCs can be recruited to tumor sites via their "homing ability".[29] This recruitment is mediated by factors like VEGF, epidermal growth factor (EGF), hepatocyte growth factor (HGF) and chemokine C-C motif chemokine ligand 2 (CCL2), which are secreted by tumor cells or activated stromal cells. Then these BM-MSCs gradually acquire the typical phenotype of CAFs and finally differentiate into CAFs.[29,30] (7) CAFs can also originate from adipocytes, vascular endothelial cells. Regulated by specific signals in

https://doi.org/10.2147/JHC.S581943

the tumor microenvironment, these two types of cells can gradually change their own phenotypic and functional characteristics, and finally transform into cells with the core properties of CAFs.[3,31]

Heterogeneity of CAFs

CAFs play a pivotal role in the TME. However, they are not a homogeneous group with uniform properties and functions. As mentioned above, CAFs have diverse origins, and CAFs of different origins carry their unique markers, exhibiting significant heterogeneity. This heterogeneity means that CAFs of different origins and subtypes show significant differences in molecular expression and function.[32]

At the molecular level, researchers analyzed a variety of selectively expressed biomarkers on the surface of CAFs in specific TME. They defined multiple CAFs phenotypes in different types of cancer, revealing the high complexity and diversity of CAFs at the phenotypic level.[33,34] CAFs in the ICC primarily express α-SMA, Actin 2, Col-Iα, PDGFR-β, Desmin, and FAP as identification markers.[24] Among these, α-SMA and FAP are the two most important CAFs markers, which can suppress antitumor immunity through multiple pathways.[34] In addition, other typical fibroblast markers, such as CD10 and Podoplanin, are also detected in ICC's CAFs, and their expression is associated with poor patient prognosis.[35] Furthermore, depending on tumor type and stage, some CAFs express unique combinations of markers, which makes their precise identification more complex.[36]

Functional heterogeneity is also a key factor in how CAFs influence tumor progression. A study using single-cell RNA sequencing technology comprehensively analyzed the human ICC transcriptome and identified six distinct fibroblast subtypes in ICC and adjacent non-tumor tissues.[37] Among these (Figure 2), myofibroblastic CAFs (mCAFs), inflammatory CAFs (iCAFs), vascular CAFs (vCAFs), antigen-presenting CAFs (apCAFs), and endothelial-like CAFs (eCAFs) are present in ICC tissue, while adipose fibroblasts are primarily distributed in adjacent precancerous lesions. α-SMA$^+$ mCAFs participate in the remodeling of the ECM, synthesizing and secreting components such as collagen and fibronectin to construct a dense matrix network.[38] On the one hand, they provide a protective barrier for tumor cells, hindering the arrival of immune cells and chemotherapy drugs to the core region of the tumor, leading to treatment resistance. On the other hand, they guide tumor cells to migrate along matrix fibers, promoting tumor metastasis. iCAFs are characterized by the secretion of cytokines such as interleukin-6 (IL-6) and tumor necrosis factor-α, which promote tumor cell proliferation; they also secrete certain growth factors, such as EGF and fibroblast growth factor, providing growth signals for tumor cells.[39] apCAFs primarily express major histocompatibility complex class II molecules. These major histocompatibility complex class II molecules activate CD4$^+$ T cells, interact with them, and play a crucial role in regulating tumor immunity.[40] vCAFs participate in regulating tumor angiogenesis by releasing factors such as VEGF, promoting tumor vascularization, and ensuring nutrient supply to tumors.[41] Additionally, a rare subpopulation of mesCAFs has been identified in ICC, originating from PFs and expressing mesothelial markers (Mesothelin, Uroplakin 1B, and Uroplakin 3B).[40] In summary, the heterogeneity of CAFs determines their role in tumor drug resistance. Different types of CAFs promote the development and progression of tumor drug resistance through multiple mechanisms. These include, but are not limited to, regulating the ECM to interfere with drug delivery, influencing metabolic reprogramming, modulating tumor immunity, and activating drug resistance signaling pathways in tumor cells.

Drug Resistance Mechanisms of CAFs

Whether it is adjuvant chemotherapy after traditional surgical resection, high-energy radiation therapy, targeted therapy, or immunotherapy targeting the TME, the presence of CAFs is like setting up a complex "obstacle network" for tumor cells. This brings great difficulties to treatment. Therefore, we will elaborate on the following four types (Figure 3) of drug resistance mechanisms.

ECM Remodeling and Physical Barrier Function

The ECM refers to the non-cellular components of tissues, composed of various macromolecules, including collagen, fibrin, glycoproteins, and proteoglycans.[42] The complex macromolecular network structure of the ECM has unique physical, biochemical, and biomechanical characteristics.[43] It undergoes extensive remodeling during tumor progression, thereby enabling communication between tumor cells and neighboring cells in the TME.[44] In general, the remodeling of the ECM manifests in two aspects: increased stiffness and degradation.[42] The increased cross-linking between ECM

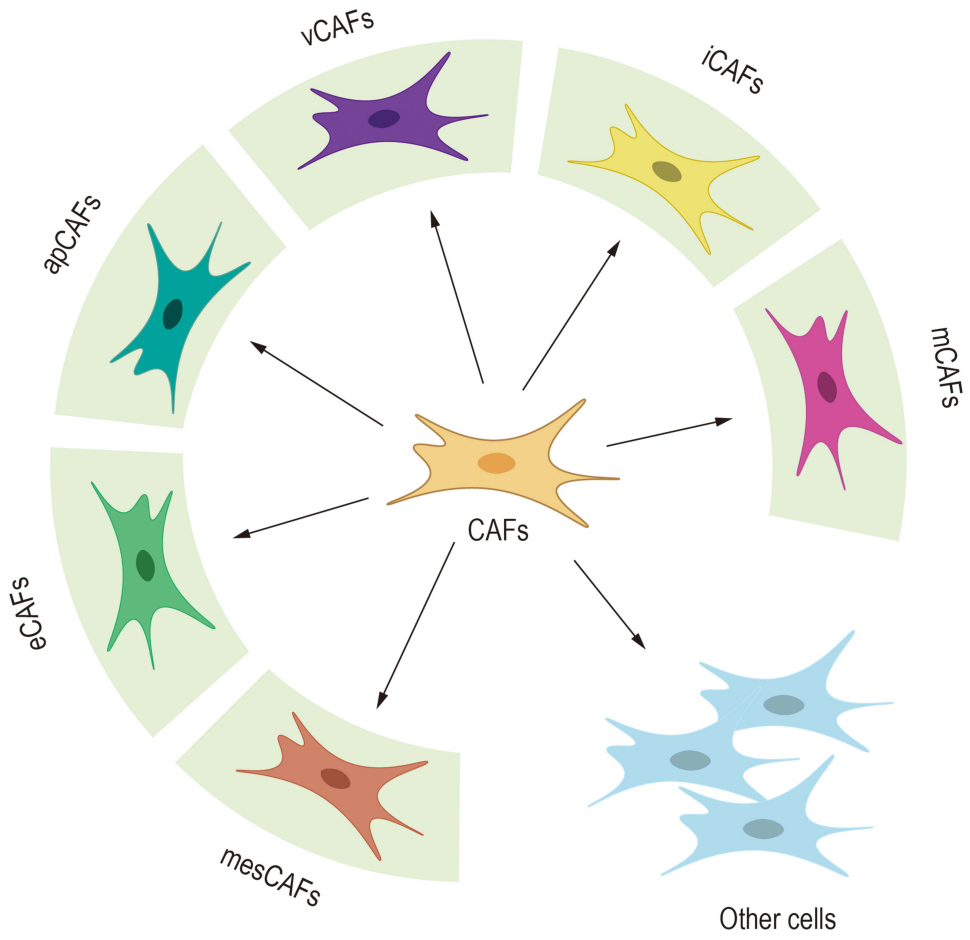

Figure 2 The functional heterogeneity and diverse types of CAFs. The central cell can differentiate into various CAF subtypes, including vCAFs, iCAFs, mCAFs, apCAFs, eCAFs, and mesCAFs. These subtypes, such as mCAFs involved in ECM remodeling, iCAFs secreting cytokines for tumor cell proliferation, apCAFs regulating tumor immunity via MHCII molecules, and vCAFs promoting tumor angiogenesis, exert distinct roles in tumor progression, including influencing drug resistance through multiple mechanisms like ECM - related drug delivery interference and activating tumor cells drug resistance signaling pathways.
Abbreviations: apCAFs, Antigen-presenting Cancer-Associated Fibroblasts; eCAFs, Epithelial Cancer-Associated Fibroblasts; iCAFs, Inflammatory Cancer-Associated Fibroblasts; mCAFs, Matrix Cancer-Associated Fibroblasts; mesCAFs, Mesothelial Cancer-Associated Fibroblasts; MHCII, Major Histocompatibility Complex Class II; vCAFs, Vascular Cancer-Associated Fibroblasts.

proteins may lead to the ECM becoming rigid, thereby limiting the diffusion and penetration of chemotherapy drugs within tumor tissue. This makes it difficult for the drugs to reach the surrounding tumor cells and exert their cytotoxic effects, thereby reducing the therapeutic efficacy of the drugs and leading to tumor cell resistance.[45] Related studies have shown that during the fibrosis process in HCC tissue, the ECM content in liver tissue increases to eight times its original level.[46] The study conclusions emphasize a significant association between increased ECM stiffness and enhanced resistance to doxorubicin in HCC patients. Conversely, the disruption of these cross-links leads to ECM degradation. Additionally, a stiff ECM can stimulate epithelial cells to transform from normal cells into malignant tumor cells,[44,47] which is associated with poor patient outcomes.

CAFs possess strong synthetic and secretory capabilities, enabling them to directly produce various ECM proteins, such as collagen, fibronectin, and laminin, among others.[48] Among these, excessive deposition and cross-linking of collagen lead to the ECM stiffening, significantly increasing interstitial fluid pressure. Such alterations in the micro-environment have been shown to hinder the effective delivery of chemotherapy and immunotherapy drugs, thereby reducing tumor treatment efficacy.[49,50] As mentioned earlier, myCAFs participate in the secretion of various ECM proteins in ICC. The key matrix proteins produced by this subtype include Col I and HA.[15] In ICC, increased secretion of Col I can enhance the stiffness of the ECM. It acts as a mechanical barrier to prevent the penetration of chemotherapy drugs. Meanwhile, in pancreatic cancer, it can reduce the influx of immune cells and inhibit the anti-tumor response.[51]

https://doi.org/10.2147/JHC.S581943

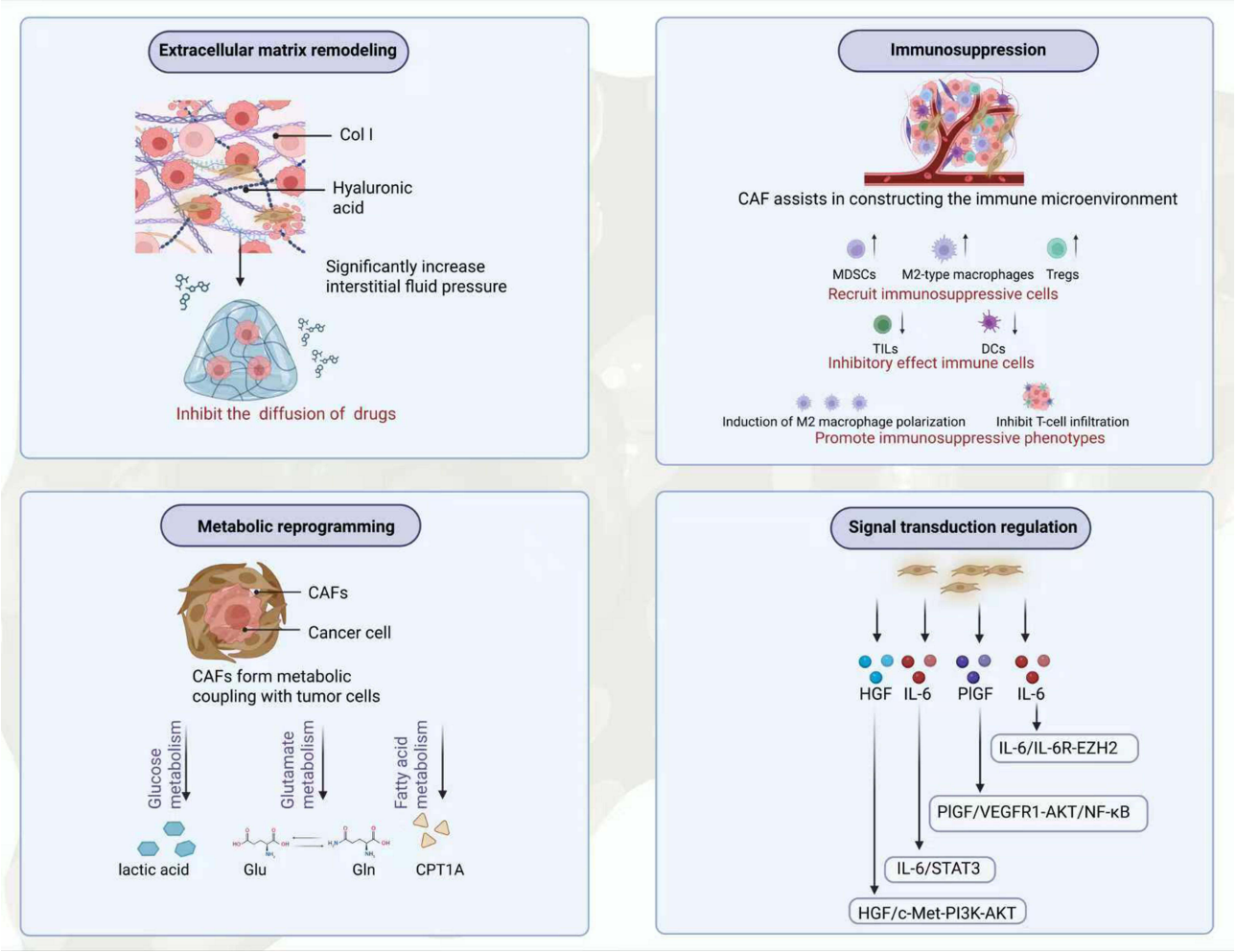

Figure 3 Four mechanisms of drug resistance mediated by CAFs in ICC. This figure illustrates the key roles of CAFs in driving drug resistance in ICC through four major mechanisms: extracellular matrix remodeling; immunosuppression; metabolic reprogramming; and signal transduction regulation. Specifically, CAFs drive extracellular matrix remodeling by secreting Col I and hyaluronic acid, which increase interstitial fluid pressure and impede drug diffusion; they construct an immunosuppressive microenvironment by recruiting MDSCs, M2-type macrophages, and Tregs, while inhibiting the function of TILs and DCs; they establish metabolic coupling with cancer cells to reprogram glucose, glutamate, and fatty acid metabolism; and they activate downstream signaling pathways such as HGF/c-Met/PI3K-AKT, IL-6/STAT3, and PlGF/VEGFR1-AKT/NF-κB to promote tumor progression and therapeutic resistance.

Abbreviations: AKT, Protein Kinase B; Col I, Collagen Type I; CPT1A, Carnitine Palmitoyltransferase 1A; DCs, Dendritic Cells; EZH2, Enhancer of Zeste Homolog 2; Glu, Glutamate; Gln, Glutamine; HGF, Hepatocyte Growth Factor; IL-6, Interleukin-6; IL-6R, Interleukin-6 Receptor; MDSCs, Myeloid-Derived Suppressor Cells; NF-κB, Nuclear Factor kappa-B; PI3K, Phosphoinositide 3-Kinase; PlGF, Placental Growth Factor; STAT3, Signal Transducer and Activator of Transcription 3; TME, Tumor Microenvironment; Tregs, Regulatory T Cells; TILs, Tumor-Infiltrating Lymphocytes; VEGFR1, Vascular Endothelial Growth Factor Receptor 1.

HA is a viscoelastic molecule with strong water-binding capacity, conferring excellent water retention and expansibility to the ECM, thereby contributing to ECM volume expansion and structural stability. As HA levels rise, the interstitial fluid pressure also increases, significantly impairing the penetration of chemotherapy drugs.[52] Previous studies have shown that HA is highly expressed in other tumor types, such as pancreatic ductal adenocarcinoma and breast cancer. This is closely associated with tumor chemotherapy resistance and poor clinical outcomes.[15] PEGPH20 is a polyethylene glycol-modified human recombinant PH20 hyaluronidase. This enzyme has been shown to rapidly and sustainably degrade HA, thereby enhancing the intratumoral delivery of gemcitabine. Compared with gemcitabine monotherapy, the combination of PEGPH20 and gemcitabine significantly reduced the incidence of metastasis and improved animal survival rates.[53] Additionally, myCAFs can produce insulin-like growth factor-binding protein-5,[54] which influences fibrogenic responses, myofibroblast transdifferentiation, and the ECM production.[55] It has been reported that ICC exhibits a significantly higher expression of insulin-like growth factor-binding protein-5 compared to normal liver tissue,

HCC, non-tumor chronic liver diseases of various types, and extrahepatic adenocarcinomas.[56] This makes it one of the specific markers for ICC and may play an important role in promoting drug resistance.

CAF-Mediated Metabolic Reprogramming

Metabolic reprogramming is one of the key characteristics of tumors. It is the process by which tumor cells remodel their metabolic networks. This helps them adapt to the altered energy demands associated with rapid proliferation, invasive metastasis and other biological behaviors.[57] The TME contains abnormally activated metabolic pathways, continuously supplying tumor cells with essential substances such as ATP, biosynthetic precursors, and reducing equivalents. This establishes a robust material and energy foundation for sustained tumor growth and drug resistance.[58]

Glucose Metabolism

Tumor cells undergo rapid glycolysis even in the presence of oxygen, consuming large amounts of glucose and secreting lactic acid, which is known as the "Warburg effect". CAFs are influenced by tumor cells also exhibit similar aerobic glycolysis, a phenomenon referred to as the reverse "Warburg effect".[59] In other words, CAFs can provide nutrients for mitochondrial oxidative phosphorylation in neighboring tumor cells through aerobic glycolysis,[60] which also contributes to tumor cell resistance. In ICC, compared to normal fibroblasts, CAFs can utilize more glucose and release more lactate.[61] Studies have shown that tumor cells expressing EGF receptor (EGFR) or HGF receptor (HGFR) exhibit increased glycolytic activity and elevated lactate levels.[62] These elevated lactate levels induce CAFs to secrete more HGF through an NF-κB-dependent mechanism. This activates HGFR-independent signaling in tumor cells, leading to their sustained resistance to tyrosine kinase inhibitor therapy.[63] Additionally, lactate can stabilize hypoxia-inducible factor-1 (HIF-1).[64] Among these, HIF-1α is a key transcription factor, it can participate in multiple biological processes when stably activated. These processes include tumor cells survival, invasion, and angiogenesis. In this way, it comprehensively promotes tumor cells survival and also enhances drug resistance.[65] A study demonstrated that HIF-1α and the hypoxia response element jointly regulate microRNA-210 expression, leading to its overexpression, which in turn arrests ICC cell proliferation at the G2/M phase and enhances their resistance to gemcitabine.[66] Furthermore, the enhanced glycolytic activity leads to more lactate and H^+ being secreted into the extracellular space. The resulting pH gradient affects how certain weakly alkaline chemotherapy drugs (like doxorubicin) are distributed and absorbed, causing physiological drug tolerance.[61]

Glutamate Metabolism

Changes in amino acid metabolism also exercise significant influence on how drug resistance develops in ICC cells.[67] Relevant studies have revealed that the metabolism of glutamine (Gln) and glutamate (Glu) is abnormally active in tumors, influencing tumor metabolism.[68] In tumors, Gln and Glu undergo dynamic bidirectional conversion via enzyme-catalyzed reactions. The core process is the conversion of Gln to Glu by glutaminases, which provides tumor cells with raw materials for glutathione synthesis and tricarboxylic acid cycle participation to support their metabolic needs.[69] Meanwhile, Glu can be reversely converted to Gln by Gln synthetase in CAFs, forming a cycle to maintain nutrient homeostasis in the tumor microenvironment, which collectively promotes tumor progression.[70] Tumor cells overexpress Gln transporters to extensively uptake Gln. Its metabolism not only provides raw materials for overactivated glycolysis and oxidative phosphorylation reactions but also regulates autophagy to induce tumor cells resistance to chemotherapy drugs.[71] Autophagy supports chemotherapy resistance by helping tumor cells overcome stress signals from the surrounding environment and intracellular stress (including nutrient deprivation and chemotherapy cytotoxicity).[72] During Gln degradation, ammonia is released as a byproduct, which can induce autophagy in surrounding CAFs. Autophagic CAFs further release Gln for tumor cells metabolism, thereby forming a positive feedback loop between tumor cells Gln dependence and CAFs conversion/autophagy.[73] Recent studies suggest that multidrug resistance in ICC may be caused by autophagy.[74] CAFs are stimulated by ammonia secreted by tumor cells. This triggers the activation of autophagy-related signals. It then leads to drug resistance in ICC patients.[75] Studies have demonstrated that inhibiting the combination of glucose transporter and targeting glutaminase in experiments can overcome the aforementioned chemotherapy resistance in ICC.[76] Therefore, inhibiting Gln/Glu metabolism may provide new intervention strategies for treating resistance in ICC.

Fatty Acid Metabolism

Tumor cells can increase fatty acid uptake and synthesis through lipid metabolism reprogramming to provide energy for themselves and build cell membranes. Research teams noted distinctions in fatty acid metabolism between therapy-responsive and drug-resistant cells, signifying this metabolic process may exert key effects on chemoresistance development.[77] On one hand, CAFs secrete lipid precursors. These reduce the unsaturated fatty acid/saturated fatty acid ratio in ICC cell membranes, lessening platinum-based drug-induced insertion damage to the membranes.[78] On the other hand, CAFs help activate the fatty acid β-oxidation pathway. They upregulate the key rate-limiting enzyme carnitine palmitoyl transferase 1A, providing ICC tumor cells with plenty of ATP and nicotinamide adenine dinucleotide phosphate.[79] ATP drives ATP-binding cassette transporters to mediate the efflux of chemotherapy drugs, significantly reducing intracellular chemotherapy drug concentrations and leading to chemotherapy resistance in ICC.[78]

CAF-Involved Regulation of Immunosuppression

The TME is a highly plastic immunosuppressive niche. Its core function is to help tumor cells evade immune surveillance, which has become a key barrier to current immunotherapy. In this process, CAFs, with their unique secretory properties, act as the core "drivers" regulating the immunosuppressive state of the tumor microenvironment. CAFs can secrete factors such as CCL2, C-X-C motif chemokine ligand 12 (CXCL12), TGF-β, IL-10 and IL-6, which promote the recruitment and function of immunosuppressive cells, including regulatory T cells, myeloid-derived suppressor cells (MDSCs), and M2-type macrophages, thereby impairing anti-tumor immune responses.[80–82] These cells secrete inhibitory cytokines like IL-10 and TGF-β, which can further suppress antitumor immune responses, disrupt immune balance in the TME, and help tumor cells evade immune system attacks.[83] They also modulate the tumor's sensitivity to immunotherapeutic agents, leading to drug resistance.

As mentioned earlier, CAFs recruit immunosuppressive MDSCs to the TME of ICC by secreting CCL2 and CXCL12. Research by He Rui's team has found that CAFs may enhance the stem cell-like properties of MDSCs, creating an optimal microenvironment for the survival and chemotherapy resistance of ICC tumor cells.[13] MDSCs suppress $CD4^+$ and $CD8^+$ T cell function, promoting tumor immune evasion and drug resistance.[84,85] Meanwhile, CAF-derived IL-6 reduces $CD8^+$ tumor-infiltrating lymphocytes and increases the number of $Foxp3^+$ tumor-infiltrating lymphocytes, further exacerbating resistance.[86] Studies found increased Polymorphonuclear-MDSCs infiltration in advanced ICC, associated with the tRNA m7G methyltransferase METTL1. When METTL1 was knocked out, the efficacy of anti-PD-1 therapy for ICC was significantly improved.[87] Moreover, CAFs recruit regulatory T cells to inhibit $CD8^+$ T cell infiltration and secrete IL-10 and TGF-β to further suppress effector T cell function, thereby fostering an immunosuppressive milieu and promoting ICC lymph node metastasis.[88] Furthermore, in mouse models of ICC, IL-6 secreted by CAFs promotes the formation of M2-type macrophages, enhances immunosuppression, and facilitates the escape of tumor cells.[89] In addition to the above, CAF-derived IL-10, TGF-β, and Prostaglandin E2 can also block the maturation and antigen-presenting capacity of dendritic cells, converting them into tolerogenic or regulatory dendritic cells.[90] Mediated by CAFs, these immune cells collectively enable tumor cells to evade immune attack, promoting ICC progression and therapeutic resistance.

Wang et al demonstrated through single-cell RNA sequencing that CAFs in ICC specifically express the bile acid receptor G protein-coupled bile acid receptor 1. Excessive bile acids can target and activate this receptor, driving CAFs to secrete high levels of CXCL10. This factor promotes ICC cell invasion and EMT via downstream pathways, while also recruiting and maintaining immature neutrophils in the tumor microenvironment through Toll-like receptor 4-mediated mechanisms. Consequently, this cascade constructs an immunosuppressive microenvironment leading to CD8+ T cell exhaustion, ultimately diminishing the efficacy of anti-PD-1 immune checkpoint inhibitors.[16]

Significant Signaling Pathways Participated by CAFs

CAFs can regulate multiple important molecular signaling pathways and secrete key cytokines to promote reprogramming, thereby contributing to chemotherapy resistance. First of all, HGF secreted by CAFs can bind to the cellular-mesenchymal to epithelial transition factor (c-Met) on the surface of tumor cells. This causes c-Met dimerization and autophosphorylation, which activates the downstream PI3K-AKT signaling pathway.[91] This process enables tumor cells

to resist chemotherapy-induced apoptosis, resulting in drug resistance. In addition, FAP^{+}CAFs derived from ICC can secrete large amounts of IL-6 and IL-33. These cytokines activate the STAT3/5-LOX signaling pathway, inducing MDSCs to release leukotriene B4.[17] This process enhances the stemness of ICC tumor cells and leads to drug resistance. Additionally, CAF derived from ICC has been shown to continuously activate the IL-6/STAT3 pathway, promoting the expression of Bcl-2 and cyclin D1, significantly enhancing tumor cells viability and reducing sensitivity to gemcitabine.[92,93] The IL-6 receptor antagonist tocilizumab can reverse this drug resistance phenomenon.[94] Meanwhile, IL-6 secreted by vCAFs significantly enhances the malignancy of ICC cells through the interaction of the IL-6/IL-6R axis between CAFs and tumor cells.[37,95] IL-6 secreted by vCAFs can upregulate enhancer of zeste homolog 2 (a protein associated with tumor malignant progression) in ICC tumor cells, thereby enhancing the malignant potential of tumor cells and promoting the malignant progression of ICC.[37] On the other hand, in a hypoxic microenvironment, CAFs derived from HSCs highly express placental growth factor (PIGF). This PIGF specifically binds to VEGF receptor 1, activating the AKT/NF-κB signaling axis and promotes CAFs to transform into myofibroblast-like phenotypes.[96] This process significantly enhances the resistance of ICC to gemcitabine combined with cisplatin treatment, while PIGF inhibitors can effectively restore chemotherapy sensitivity.[97] Furthermore, in vitro modeling of ICC-CAF crosstalk demonstrated that CAFs express insulin-like growth factor 2, activating the insulin receptor/insulin-like growth factor 1 receptor signaling pathway in ICC tumor cells to protect them from the harmful effects of erlotinib.[98] Overall, these findings not only reveal the molecular basis of how CAFs promote ICC chemotherapy resistance, but also provide an important theoretical basis for developing new combination therapy strategies that target CAFs.

Therapeutic Strategies Targeting CAFs

In the treatment of ICC, CAF-mediated drug resistance significantly impairs therapeutic efficacy. Therefore, developing targeted strategies against CAFs to break through the bottleneck of treatment resistance has become a critical unmet clinical need. Currently, two core and feasible targeted intervention approaches have been established for CAF-mediated drug resistance: first, inhibiting the activation and generation of CAFs to reduce their abnormal accumulation in the TME (Table 1); second, directly targeting the pro-tumorigenic functions of CAFs (Table 2). Based on the above insights, this review systematically elaborated on the aforementioned four strategies as follows: (1) Inhibiting the secretion of ECM-related components to disrupt the abnormal remodeling of ECM and its physical barrier function, thereby reversing the drug-resistant phenotype of ICC. (2) Targeting CAF-induced metabolic reprogramming processes (encompassing key pathways such as glycolysis, glutamine metabolism, and fatty acid metabolism) by blocking the nutrient transport and metabolic support from CAFs to tumor cells, cutting off the energy supply and biosynthetic raw material sources of tumor cells. This not only significantly inhibits the proliferative activity and drug resistance potential of tumor cells but also enhances the cytotoxic sensitivity of tumor cells to chemotherapeutic agents and targeted therapies, improving the overall therapeutic effect. (3) Targeting the immunosuppressive state in the TME to restore the tumor-killing activity of immune cells, enhance antitumor immune responses, and boost the efficacy of comprehensive treatment. (4) Interfering

Table 1 Inhibition of CAF Activation and Generation

Drug Name	Biomarkers	Therapeutic Targets	Mechanisms of Action
Galunisertib	TGF-β	TGF-β	Inhibit CAF activation by targeting TGF-β
Imatinib, Sunitinib	PDGF, PDGFR	PDGFR	Block PDGF receptor to inhibit CAF activation
Biejia Ruangan Pian (BJRG)	α-SMA, Col I	α-SMA, Col I	Downregulate α-SMA and Col I, thereby inhibiting CAF activation
B7-33-SNPs	α-SMA, CD31, VEGFA, ANG2, RXFP1	TGF-β Pathway, VEGFR2, RXFP1 receptor	Targets CAFs and angiogenesis in ICC, inhibiting CAF activation and improving tumor permeability.
Metformin	CAV-1, HIF-1α, TGF-β, IL-6	AMPK, NF-κB, TGF-β pathway, HIF-1α	Upregulates CAV-1, inhibits TGF-β and NF-κB pathways, and downregulates HIF-1α to block CAF differentiation, autocrine activation, and hypoxia-induced generation

https://doi.org/10.2147/JHC.S581943

Table 2 Inhibition of CAF Functions

Drug Name	Biomarkers	Therapeutic Targets	Mechanisms of Action
Tocilizumab	IL-6, sIL-6R	IL-6R	Block IL-6 receptor to inhibit CAF secretion function
Cabozantinib	HGF, MET	HGF/MET signaling pathway	Block HGF/MET signaling pathway to inhibit CAF secretion function
Resveratrol	IL-6, N-cadherin/ E-cadherin	IL-6	Inhibit CAF secretion of IL-6
β-aminopropionitrile	LOX, Collagen	LOX	Inhibit collagen cross-linking by targeting LOX
Simtuzumab (GS-6624)	LOXL2, Collagen cross-linking level	LOXL2	Inhibit collagen cross-linking by targeting LOXL2
PEGPH20	HA, Gemcitabine concentration	HA	Promote tumor vascular reperfusion by targeting HA, improve the tumor penetration and cytotoxicity of chemotherapy drugs
Venetoclax (ABT-199), Navitoclax (ABT-263)	PDGF/PDGFR	PDGF/PDGFR axis (BH3 mimics)	Enhance CAF sensitivity to apoptosis, reduce the number of myCAFs in the tumor microenvironment, and inhibit tumor growth
Cilengitide	Integrin αvβ3	Integrin αvβ3	Inhibit CAF-tumor cells interactions by targeting integrin αvβ3, enhance tumor cells sensitivity to chemotherapy
Defactinib (VS-6063)	FAK, Survival-related proteins	FAK	Block CAF-mediated tumor cells survival signaling pathways by targeting FAK
Biejia Ruangan Pian (BJRG)	YAP/TAZ, mTOR activity marker	HIPPO/AKT/mTOR signaling pathway	Exert synergistic effects through multiple mechanisms by inhibiting the HIPPO/ AKT/mTOR signaling pathway
2-deoxy-D-glucose	GLUT1/HK2, Lactate	CAF glycolysis	Inhibit CAF metabolic reprogramming by targeting glycolysis
Telaglenastat (CB-839)	GLS, Gln consumption rate	CAF glutaminase	Inhibit CAF metabolic reprogramming by targeting glutaminase
Curcumin	LAT2, Gln level in tumor cells	LAT2/Gln pathway	Target the LAT2/Gln pathway, cut off Gln supply to tumor cells, weaken the metabolic support role of CAFs
Losmapimod (GNE-140)	LDHA, Lactate secretion rate	CAF lactate dehydrogenase A	Inhibit CAF-mediated lactate secretion by targeting lactate dehydrogenase A, hinder tumor cell survival and invasion
Bortezomib, CXCR4 inhibitor, Checkpoint inhibitor	CXCR4, PD-L1	CXCR4, Immune checkpoint	CXCR4 inhibitors suppress the ECM to enhance bortezomib's ability to kill tumor cells through immune surveillance; checkpoint inhibitors further amplify the therapeutic effect
AZD3965	Accumulated lactic acid quantity	MCT1	Block the efflux of lactic acid from CAFs to tumor cells, and reducing the dependence of tumor cells on oxidative phosphorylation
Orlistat derivatives	FASN	FASN, lipid metabolism	Reduce the lipid support of CAFs to tumor cells and their own energy reserves
Plerixafor (AMD3100)	CXCR4, N-cadherin, VEGF-C and MMP-9	The binding of CXCL12 to CXCR4	Inhibiting the anti-apoptotic signals in tumor cells reduces the recruitment of MDSCs and tumor-associated macrophages
Lirafugratinib (RLY-4008)	FGFR2 Fusion Protein, α-SMA, Col III	FGFR2	Inhibits abnormal FGFR2 signaling in CAFs, blocks CAF-iCCA cell crosstalk, and reverses targeted therapy resistance.
Samrotamab Vedotin (ABBV-085)	LRRC15, TGF-β	LRRC15	Targets LRRC15, a surface marker of CAFs, and delivers monomethyl auristatin E via antibody-drug conjugate technology to kill CAFs, disrupt the tumor-supportive stromal microenvironment, and enhance tumor immune infiltration.
Dichloroacetate	PDK, Lactate	PDK	Reverses the Warburg effect in CAFs and remodels CAF mitochondrial metabolism via the PDK/PDH axis.
Metformin	MCT4, 2HG, HK2, LDH, IL-6, CXCL12, IDO	AMPK, Mitochondrial Complex I, MCT4, PI3K/AKT/ mTOR, NF-κB	Activates AMPK, inhibits mitochondrial Complex I and key signaling pathways, blocks MCT4-mediated lactate transport, and reduces secretion of immunosuppressive factors to suppress CAF metabolic reprogramming, immune suppression, ECM remodeling, and signal crosstalk with tumor cells
Losartan	α-SMA, Col I, TGF-β	AT1R	Targets the TGF-β signaling pathway in CAFs, reduces the number of α-SMA +CAFs and type I collagen deposition, decreases tumor stromal pressure, and lowers ECM stiffness.

with the paracrine signaling crosstalk between CAFs and tumor cells by blocking the cross-activation of key signaling pathways between them, inhibiting the abnormal expression of key drug resistance-related genes in tumor cells as well as the continuous transmission of malignant proliferation and invasion signals, and disrupting the pro-tumorigenic vicious cycle formed by CAFs and tumor cells, thereby fundamentally abolishing the molecular basis of drug resistance. These intervention strategies, starting from the dual dimensions of "source control" and "functional blocking" of CAFs, can

effectively weaken the core promotional role of CAFs in tumor progression and drug resistance, providing important therapeutic directions for reversing CAF-mediated drug resistance in ICC (Figure 4).

Inhibition of CAF Activation and Generation

The activation of CAFs is typically driven by growth factors such as TGF-β, PDGF secreted by tumor cells. These cytokines promote the proliferation and functional activation of CAFs by activating signaling pathways such as SMAD, PI3K/AKT, and MAPK in CAFs.[99] Among these, TGF-β plays a key role in CAF activation.[100] TGF-β inhibitors like Galunisertib (LY2157299) have shown potential in clinical trials.[101] They can inhibit CAF activation and reverse tumor

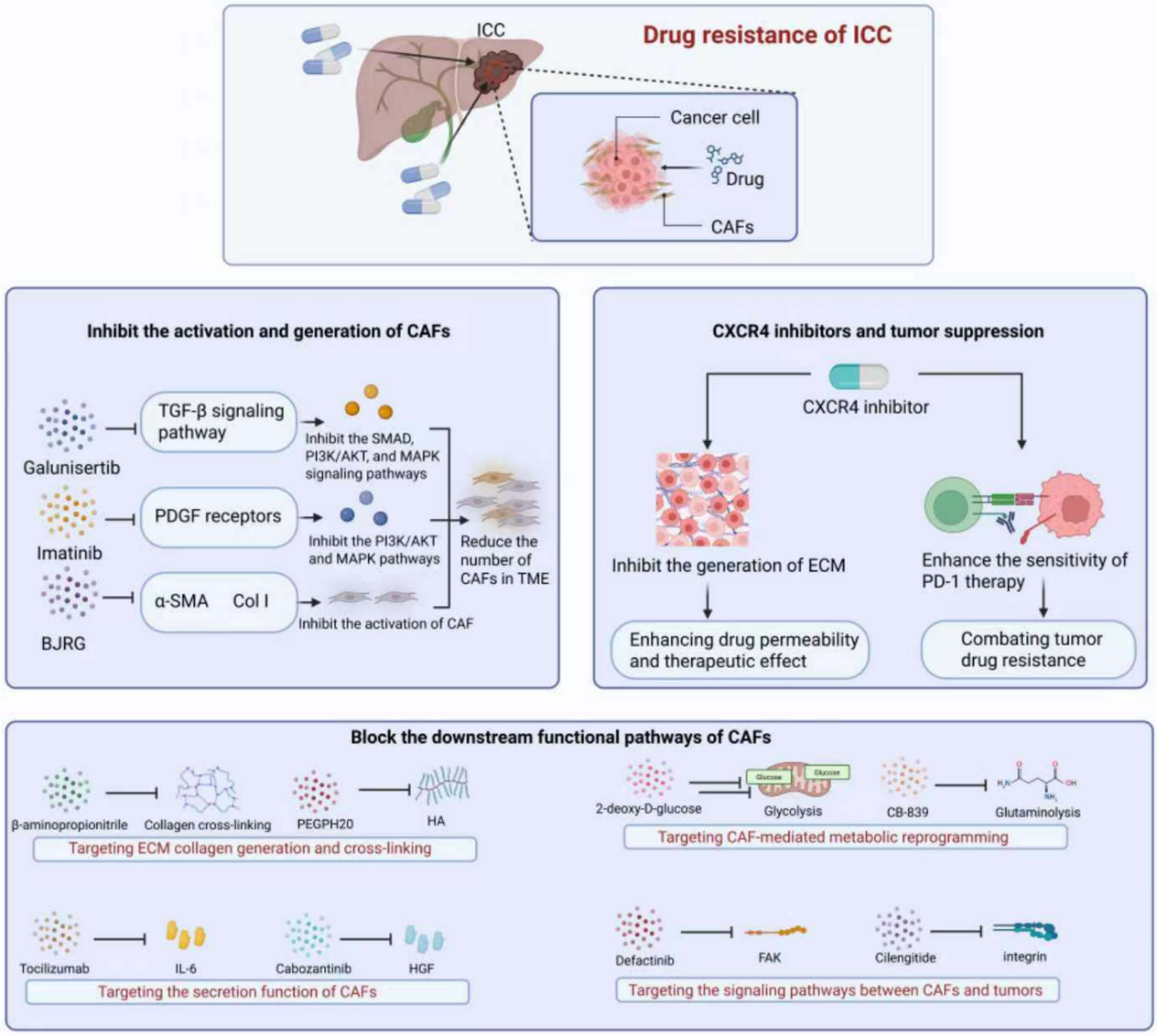

Figure 4 Targeted intervention strategies to overcome CAF-mediated drug resistance in ICC. This figure illustrates the therapeutic strategies for overcoming drug resistance in ICC by targeting CAFs, which are categorized into two main approaches: inhibiting the activation and generation of CAFs, and blocking the downstream functional pathways of CAFs. Specifically, inhibiting CAF activation and generation involves targeting the TGF-β signaling pathway (e.g., Galunisertib), PDGF receptors (e.g., Imatinib), and CAF activation markers (e.g., BJRG), thereby reducing CAF accumulation in the TME. Additionally, CXCR4 inhibitors suppress ECM generation, enhance drug permeability, and improve the sensitivity of anti-PD-1 therapy to combat drug resistance. Blocking downstream pathways includes strategies such as targeting ECM collagen generation and cross-linking (e.g., β-aminopropionitrile, PEGPH20), CAF-mediated metabolic reprogramming (e.g., 2-deoxy-D-glucose, CB-839), CAF secretion function (e.g., Tocilizumab, Cabozantinib), and signaling pathways between CAFs and tumors (e.g., Defactinib, Cilengitide), ultimately reversing therapeutic resistance in ICC.
Abbreviations: α-SMA, alpha-Smooth Muscle Actin; AKT, Protein Kinase B; Col I, Collagen Type I; CXCR4, C-X-C chemokine receptor 4; ECM, Extracellular Matrix; FAK, Focal Adhesion Kinase; HGF, Hepatocyte Growth Factor; IL-6, Interleukin-6; MAPK, Mitogen-Activated Protein Kinase; PDGF, Platelet-Derived Growth Factor; PI3K, Phosphoinositide 3-Kinase; SMAD, Mothers Against Decapentaplegic Homolog; TGF-β, Transforming Growth Factor-beta; TME, Tumor Microenvironment.

https://doi.org/10.2147/JHC.S581943

resistance. Additionally, PDGFR inhibitors such as Imatinib and Sunitinib have been used to inhibit CAF activation, thereby reducing fibrosis and immune suppression in the tumor microenvironment.[102] Furthermore, Biejia Ruangan Pian (BJRG) (a traditional Chinese herbal medicine) is widely used for treating liver diseases. In vitro experiments have shown that this drug can significantly downregulate α-SMA and Col I, thereby inhibiting CAF activation.[103]

Inhibition of CAF Functions

Targeting Collagen Production and Crosslinking

Drugs targeting collagen synthesis and cross-linking can significantly reduce the stiffness of the tumor microenvironment, thereby inhibiting tumor cells invasion and drug resistance. For example, lysyl oxidase (LOX) inhibitors such as β-aminopropionitrile and lysyl oxidase-like 2 (LOXL2) inhibitors such as Simtuzumab (GS-6624) have demonstrated efficacy in preclinical studies in inhibiting collagen cross-linking and reducing tumor fibrosis.[104] PEGPH20, a HA inhibitor, promotes tumor vascular reperfusion, improving the tumor penetration and cytotoxicity of chemotherapy drugs such as gemcitabine.[53]

Targeting CAF-Mediated Metabolic Reprogramming

Metabolic reprogramming targeting CAFs has emerged as a promising therapeutic strategy in recent years. As mentioned above, CAFs undergo significant metabolic reprogramming in the tumor microenvironment. Including enhanced glycolysis, Gln metabolism and adaptive remodeling of fatty acid metabolism, which supports tumor cells and maintains the pro-cancer microenvironment. Glycolysis inhibitors such as 2-deoxy-D-glucose and glutaminase inhibitors like CB-839 have demonstrated efficacy in inhibiting CAFs metabolic reprogramming in clinical trials, thereby reversing tumor cell resistance.[105,106] Additionally, lactate dehydrogenase A inhibitors like GNE-140 are used to inhibit CAF-mediated lactate secretion. This suppression helps hinder tumor cell survival and invasion.[107] In addition, AZD3965, a selective inhibitor of monocarboxylate transporter 1, can block the lactic acid efflux from CAFs to tumor cells, disrupt metabolic coupling, and ultimately reduce the reliance of tumor cells on oxidative phosphorylation, thereby decreasing the survival rate of tumor cells.[108] Both of the above drugs reduce the lactic acid supplied by CAFs to tumor cells, thereby disrupting the metabolic coupling on which the reverse "Warburg effect" relies and exerting therapeutic effects. Curcumin is a natural polyphenolic compound extracted from the rhizomes of the turmeric plant, known for its antitumor, anti-inflammatory, and antioxidant properties. Existing studies have found that Curcumin synergistically enhances the efficacy of gemcitabine in ICC patients resistant to gemcitabine.[109] Curcumin can target the LAT2/Gln pathway and inhibit LAT2 transport activity. This cuts off Gln supply to tumor cells and weakens the metabolic support role of CAFs.[110] Meanwhile, lipid metabolism-targeting agents represented by fatty acid synthase inhibitors disrupt lipid metabolic pathways in cancer cells, providing a highly promising strategy for targeting the metabolic hallmarks of tumor cells and achieving tumor growth suppression.[111] This reduces CAFs' lipid support for tumor cells and their own energy reserves. Together, these interventions effectively reverse the drug resistance of tumor cells caused by the metabolic support from CAFs.

Targeting CAF Secretion

Targeting the secretory function of CAFs is another important therapeutic strategy. As mentioned earlier, CAFs promote tumor cells survival, invasion, and drug resistance by secreting IL-6, HGF, VEGF, and ECM components (such as collagen and fibronectin).[112] For example, the IL-6 receptor inhibitor tocilizumab[93] and the HGF/MET signaling pathway inhibitor cabozantinib[113] can inhibit CAF secretion function. They may reverse tumor cells resistance to chemotherapy and targeted therapy.[114] Additionally, studies have found that resveratrol can inhibit CAF secretion of IL-6.[89] Conditioned medium prepared from resveratrol-pretreated CAFs can completely block tumor cells motility, restore the normal conversion of N-cadherin to E-cadherin in migrating cells, and stimulate tumor cells autophagy.[114] Thus, this drug shows promise in enhancing ICC treatment efficacy and overcoming resistance. AMD3100, an antagonist of C-X-C chemokine receptor 4 (CXCR4), can block the binding of CXCL12 to CXCR4 on tumor cells when used in combination with gemcitabine.[115] This further inhibits the anti-apoptotic signaling in tumor cells and reduces the recruitment of MDSCs and tumor-associated macrophages, making it a promising optional therapeutic approach for ICC.

Targeting Signaling Pathways Between CAFs and Tumor Cells

Targeting the interactions between CAFs and tumor cells is another key strategy for overcoming tumor resistance. The PDGF/PDGFR axis is a well-researched pathway in the ICC between tumor cells and CAFs.[116] Among these, BH3 mimics such as ABT-199 and navitoclax can enhance CAF sensitivity to apoptosis, reduce the number of myCAFs in the tumor microenvironment, and inhibit tumor growth.[35] Besides, EGFR pathway-related drugs can achieve targeted therapy by focusing on the interaction between CAFs and ICC tumor cells. They block a specific process: EGFR ligands produced by CAFs activate EGFR in tumor cells, which then induces migration, invasion, and malignant cycles to inhibit tumor growth.[35] In addition, integrin αvβ3 inhibitor cilengitide has demonstrated efficacy in clinical trials in inhibiting CAF-tumor cells interactions, thereby enhancing tumor cells sensitivity to chemotherapy.[117] Additionally, focal adhesion kinase (FAK) inhibitors such as Defactinib (VS-6063) have been used to block CAF-mediated tumor cells survival signaling pathways.[118] Furthermore, BJRG can also exert effects synergistically through multiple mechanisms by inhibiting the HIPPO/AKT/mTOR signaling pathway. This allows it to effectively inhibit tumor progression.[103]

Exploration of Novel Triple Therapy

Additionally, during the 2023 Digestive Disease Week in the United States, Li et al proposed a novel triple therapy[119] This therapy targets tumor resistance in ICC and combines bortezomib, a CXCR4 inhibitor, and a checkpoint inhibitor. Researchers performed experiments using patient-derived organoids and mouse models, and the results revealed that the resistance of patient-derived organoids to bortezomib is associated with CXCR4 overexpression. However, CXCR4 inhibitors can reverse this resistance and boost sensitivity to PD-1 therapy. Studies showed that CXCR4 inhibitors can suppress the ECM, enhancing bortezomib's ability to kill tumor cells through immune surveillance, while checkpoint inhibitors further amplify the therapeutic effect. This therapy offers a new direction for overcoming ICC resistance, but its clinical translation potential still requires further validation.[119]

Conclusion

CAFs play a crucial role in the drug resistance of ICC. On one hand, CAFs remodel the ECM. They not only provide physical support for tumor cells but also block the penetration of chemotherapeutic drugs, directly resulting in drug resistance. At the metabolic level, CAFs form metabolic coupling with tumor cells. They supply energy and substances required for proliferation, maintain metabolic homeostasis under chemotherapeutic pressure, and promote the development of drug resistance. Meanwhile, CAFs secrete various cytokines and growth factors. These activate key signaling pathways within tumor cells, enhancing their chemoresistance in multiple ways. In terms of immune regulation, CAFs create an immunosuppressive microenvironment. They help tumor cells evade immune surveillance by inhibiting the activity of immune cells and promoting the accumulation of immunosuppressive cells. Notably, CAFs subtypes such as myCAFs and iCAFs exhibit highly heterogeneous functions. However, their specific mechanisms of action in ICC drug resistance remain unclear. Therefore, studying the functional differences among these subtypes is of great significance for patients with ICC drug resistance. Current drug therapies targeting CAFs bring new hope for overcoming ICC drug resistance. They block the induction of tumor drug resistance by targeting specific functions or signaling pathways of CAFs. Yet, existing drugs face challenges like insufficient specificity, limited effectiveness, and potential side effects. Future research is needed to further explore the molecular biological characteristics of CAFs, optimize treatment regimens, and identify new targets to improve the therapeutic efficacy and prognosis of ICC patients.

Abbreviations

apCAF, Antigen-presenting CAF; BJRG, Biejia Ruangan Pian; BM-MSCs, Bone Marrow-derived Mesenchymal Stem Cells; CAFs, Cancer-Associated Fibroblasts; CCL2, C-C motif chemokine ligand 2; CCA, Cholangiocarcinoma; Col I, Type I collagen; CXCL12, C-X-C motif chemokine ligand 12; CXCR4, C-X-C chemokine receptor 4; ECM, Extracellular Matrix; EGF, Epidermal Growth Factor; EGFR, Epidermal Growth Factor Receptor; EMT, Epithelial-to-Mesenchymal Transition; eCAF, Epithelial-associated CAF; FAK, Focal Adhesion Kinase; FAP, Fibroblast Activation Protein; Gln, Glutamine; Glu, Glutamate; HA, Hyaluronic Acid; HCC, Hepatocellular carcinoma; HGFR, Hepatocyte

Growth Factor Receptor; HGF, Hepatocyte Growth Factor; HIF-1, Hypoxia-Inducible Factor-1; HSCs, Hepatic Stellate Cells; ICC, Intrahepatic Cholangiocarcinoma; iCAF, Inflammatory CAF; IL-6, Interleukin-6; LOX, Lysyl Oxidase; LOXL2, Lysyl Oxidase-Like 2; MDSCs, Myeloid-Derived Suppressor Cells; mCAF, Myofibroblastic CAF; PFs, Portal Fibroblasts; PDGF, Platelet-Derived Growth Factor; PDGFR-β, Platelet-Derived Growth Factor Receptor-β; PIGF, Placental Growth Factor; TGF-β, Transforming Growth Factor-β; TME, Tumor Microenvironment; VEGF, Vascular Endothelial Growth Factor; vCAF, Vascular CAF; c-MET, cellular-Mesenchymal to Epithelial Transition factor; α-SMA, α-Smooth Muscle Actin.

Author Contributions

Yimeng Yuan and Ruoyu Zhang are co-first authors. All authors have contributed significantly to the work described in this paper, with involvement in the conception, study design, execution, data collection, analysis and interpretation, either in individual areas or across the full scope of the work. Each author has taken part in drafting, revising, or critically evaluating the manuscript; has given final approval of the publication-ready version; has consented to the journal selected for manuscript submission; and agrees to be accountable for all elements of the presented work.

Funding

Liming Wang is supported by the CAMS Innovation Fund for Medical Sciences (CIFMS), 2022-I2M-C&T-B-062 and National Natural Science Foundation of China (ID: 82472679).

Disclosure

The authors declare that they have no conflict of interest.

References

1. Soares KC, Jolissaint JS, McIntyre SM, et al. Hepatic disease control in patients with intrahepatic cholangiocarcinoma correlates with overall survival. *Cancer Med*. 2023;12(11):12272–12284. doi:10.1002/cam4.5925
2. Moris D, Palta M, Kim C, Allen PJ, Morse MA, Lidsky ME. Advances in the treatment of intrahepatic cholangiocarcinoma: an overview of the current and future therapeutic landscape for clinicians. *CA Cancer J Clin*. 2023;73(2):198–222. doi:10.3322/caac.21759
3. Affo S, Nair A, Brundu F, et al. Promotion of cholangiocarcinoma growth by diverse cancer-associated fibroblast subpopulations. *Cancer Cell*. 2021;39(6):866–882.e811. doi:10.1016/j.ccell.2021.03.012
4. Li J, Liang Y-B, Wang Q-B, et al. Tumor-associated lymphatic vessel density is a postoperative prognostic biomarker of hepatobiliary cancers: a systematic review and meta-analysis. *Front Immunol*. 2025;15. doi:10.3389/fimmu.2024.1519999
5. Nevermann N, Bode J, Vischer M, et al. A surgical strategy for intrahepatic cholangiocarcinoma - the hilar first concept. *Langenbecks Arch Surg*. 2023;408(1):296. doi:10.1007/s00423-023-03023-y
6. Bagante F, Spolverato G, Weiss M, et al. Defining long-term survivors following resection of intrahepatic cholangiocarcinoma. *J Gastrointestinal Surg*. 2017;21(11):1888–1897. doi:10.1007/s11605-017-3550-7
7. Martin-Serrano MA, Kepecs B, Torres-Martin M, et al. Novel microenvironment-based classification of intrahepatic cholangiocarcinoma with therapeutic implications. *Gut*. 2023;72(4):736–748. doi:10.1136/gutjnl-2021-326514
8. Sha M, Jeong S, Qiu BJ, et al. Isolation of cancer-associated fibroblasts and its promotion to the progression of intrahepatic cholangiocarcinoma. *Cancer Med*. 2018;7(9):4665–4677. doi:10.1002/cam4.1704
9. Rimini M, Fornaro L, Rizzato MD, et al. Durvalumab plus gemcitabine and cisplatin in advanced biliary tract cancer: a large real-life worldwide population. *Eur J Cancer*. 2024;208:114199. doi:10.1016/j.ejca.2024.114199
10. Rizzolio S, Giordano S, Corso S. The importance of being CAFs (in cancer resistance to targeted therapies). *J Exp Clin Cancer Res*. 2022;41(1):319.
11. Høgdall D, Lewinska M, Andersen JB. Desmoplastic tumor microenvironment and immunotherapy in cholangiocarcinoma. *Trends Cancer*. 2018;4(3):239–255. doi:10.1016/j.trecan.2018.01.007
12. Chen X-M, Liang Y-B, Zuo J-X, et al. ZG16B: a key regulator of tumor progression and immune microenvironment modulation in cancer (Review). *Int J Mol Med*. 2026;57(3). doi:10.3892/ijmm.2026.5729
13. Lin Y, Cai Q, Chen Y, et al. CAFs shape myeloid-derived suppressor cells to promote stemness of intrahepatic cholangiocarcinoma through 5-lipoxygenase. *Hepatology*. 2022;75(1):28–42. doi:10.1002/hep.32099
14. Ravichandra A, Bhattacharjee S, Affò S. Cancer-associated fibroblasts in intrahepatic cholangiocarcinoma progression and therapeutic resistance. *Adv Cancer Res*. 2022;156:201–226.
15. Affò S, Sererols-Viñas L, Garcia-Vicién G, Cadamuro M, Chakraborty S, Sirica AE. Cancer-associated fibroblasts in intrahepatic cholangiocarcinoma: insights into origins, heterogeneity, lymphangiogenesis, and peritoneal metastasis. *Am J Pathol*. 2025;195(3):378–396. doi:10.1016/j.ajpath.2024.07.009
16. Huang F, Liu Z, Song Y, et al. Bile acids activate cancer-associated fibroblasts and induce an immunosuppressive microenvironment in cholangiocarcinoma. *Cancer Cell*. 2025;43(8):1460–1475.e1410. doi:10.1016/j.ccell.2025.05.017

17. Ying F, Chan MSM, Lee TKW. Cancer-associated fibroblasts in hepatocellular carcinoma and cholangiocarcinoma. *Cell Mol Gastroenterol Hepatol*. 2023;15(4):985–999. doi:10.1016/j.jcmgh.2023.01.006
18. Sirica AE, Campbell DJ, Dumur CI. Cancer-associated fibroblasts in intrahepatic cholangiocarcinoma. *Curr Opin Gastroenterol*. 2011;27 (3):276–284. doi:10.1097/MOG.0b013e32834405c3
19. Yamamoto Y, Kasashima H, Fukui Y, Tsujio G, Yashiro M, Maeda K. The heterogeneity of cancer-associated fibroblast subpopulations: their origins, biomarkers, and roles in the tumor microenvironment. *Cancer Sci*. 2023;114(1):16–24. doi:10.1111/cas.15609
20. Zhou Y, Ren H, Dai B, et al. Hepatocellular carcinoma-derived exosomal miRNA-21 contributes to tumor progression by converting hepatocyte stellate cells to cancer-associated fibroblasts. *J Exp Clin Cancer Res*. 2018;37(1):324. doi:10.1186/s13046-018-0965-2
21. Li R, Huang B, Tian H, Sun Z. Immune evasion in esophageal squamous cell cancer: from the perspective of tumor microenvironment. *Front Oncol*. 2022;12:1096717. doi:10.3389/fonc.2022.1096717
22. Wang Y, Li G, Wang H, Qi Q, Wang X, Lu H. Targeted therapeutic strategies for Nectin-4 in breast cancer: recent advances and future prospects. *Breast*. 2025;79:103838. doi:10.1016/j.breast.2024.103838
23. Zhang Y, Weinberg RA. Epithelial-to-mesenchymal transition in cancer: complexity and opportunities. *Front Med*. 2018;12(4):361–373. doi:10.1007/s11684-018-0656-6
24. Osman A, Afify SM, Hassan G, Fu X, Seno A, Seno M. Revisiting cancer stem cells as the origin of cancer-associated cells in the tumor microenvironment: a hypothetical view from the potential of iPSCs. *Cancers*. 2020;12(4):879. doi:10.3390/cancers12040879
25. Radisky DC, Kenny PA, Bissell MJ. Fibrosis and cancer: do myofibroblasts come also from epithelial cells via EMT? *J Cell Biochem*. 2007;101 (4):830–839. doi:10.1002/jcb.21186
26. Wu H, Chen C, Ziani S, et al. Fibrotic events in the progression of cholestatic liver disease. *Cells*. 2021;10(5):1107. doi:10.3390/cells10051107
27. Itou RA, Uyama N, Hirota S, et al. Immunohistochemical characterization of cancer-associated fibroblasts at the primary sites and in the metastatic lymph nodes of human intrahepatic cholangiocarcinoma. *Human Pathol*. 2019;83:77–89. doi:10.1016/j.humpath.2018.08.016
28. Hosaka K, Yang Y, Seki T, et al. Pericyte-fibroblast transition promotes tumor growth and metastasis. *Proc Natl Acad Sci USA*. 2016;113(38): E5618–5627. doi:10.1073/pnas.1608384113
29. Cirri P, Chiarugi P. Cancer associated fibroblasts: the dark side of the coin. *Am J Cancer Res*. 2011;1(4):482–497.
30. Rubinstein-Achiasaf L, Morein D, Ben-Yaakov H, et al. Persistent inflammatory stimulation drives the conversion of MSCs to inflammatory CAFs that promote pro-metastatic characteristics in breast cancer cells. *Cancers*. 2021;13(6):1472. doi:10.3390/cancers13061472
31. Kidd S, Spaeth E, Watson K, et al. Origins of the tumor microenvironment: quantitative assessment of adipose-derived and bone marrow-derived stroma. *PLoS One*. 2012;7(2):e30563. doi:10.1371/journal.pone.0030563
32. Chhabra Y, Weeraratna AT. Fibroblasts in cancer: unity in heterogeneity. *Cell*. 2023;186(8):1580–1609. doi:10.1016/j.cell.2023.03.016
33. Costa A, Kieffer Y, Scholer-Dahirel A, et al. Fibroblast heterogeneity and immunosuppressive environment in human breast cancer. *Cancer Cell*. 2018;33(3):463–479.e410. doi:10.1016/j.ccell.2018.01.011
34. Mao X, Xu J, Wang W, et al. Crosstalk between cancer-associated fibroblasts and immune cells in the tumor microenvironment: new findings and future perspectives. *Mol Cancer*. 2021;20(1):131. doi:10.1186/s12943-021-01428-1
35. Vaquero J, Aoudjehane L, Fouassier L. Cancer-associated fibroblasts in cholangiocarcinoma. *Curr Opin Gastroenterol*. 2020;36(2):63–69. doi:10.1097/MOG.0000000000000609
36. Zhao Z, Li T, Yuan Y, Zhu Y. What is new in cancer-associated fibroblast biomarkers? *Cell Commun Signal*. 2023;21(1):96. doi:10.1186/s12964-023-01125-0
37. Zhang M, Yang H, Wan L, et al. Single-cell transcriptomic architecture and intercellular crosstalk of human intrahepatic cholangiocarcinoma. *J Hepatol*. 2020;73(5):1118–1130. doi:10.1016/j.jhep.2020.05.039
38. Piersma B, Hayward MK, Weaver VM. Fibrosis and cancer: a strained relationship. *Biochim Biophys Acta Rev Cancer*. 2020;1873(2):188356. doi:10.1016/j.bbcan.2020.188356
39. Kennel KB, Bozlar M, De Valk AF, Greten FR. Cancer-associated fibroblasts in inflammation and antitumor immunity. *Clin Cancer Res*. 2023;29(6):1009–1016. doi:10.1158/1078-0432.CCR-22-1031
40. Minini M, Fouassier L. Cancer-associated fibroblasts and extracellular matrix: therapeutical strategies for modulating the cholangiocarcinoma microenvironment. *Current Oncol*. 2023;30(4):4185–4196. doi:10.3390/curroncol30040319
41. Zhang H, Yue X, Chen Z, et al. Define cancer-associated fibroblasts (CAFs) in the tumor microenvironment: new opportunities in cancer immunotherapy and advances in clinical trials. *Mol Cancer*. 2023;22(1):159. doi:10.1186/s12943-023-01860-5
42. Arriazu E, Ruiz de Galarreta M, Cubero FJ, et al. Extracellular matrix and liver disease. *Antioxid Redox Signaling*. 2014;21(7):1078–1097. doi:10.1089/ars.2013.5697
43. Lu P, Weaver VM, Werb Z. The extracellular matrix: a dynamic niche in cancer progression. *J Cell Biol*. 2012;196(4):395–406. doi:10.1083/jcb.201102147
44. Najafi M, Farhood B, Mortezaee K. Extracellular matrix (ECM) stiffness and degradation as cancer drivers. *J Cell Biochem*. 2019;120 (3):2782–2790. doi:10.1002/jcb.27681
45. Feng X, Cao F, Wu X, Xie W, Wang P, Jiang H. Targeting extracellular matrix stiffness for cancer therapy. *Front Immunol*. 2024;15:1467602. doi:10.3389/fimmu.2024.1467602
46. Calitz C, Rosenquist J, Degerstedt O, et al. Influence of extracellular matrix composition on tumour cell behaviour in a biomimetic in vitro model for hepatocellular carcinoma. *Sci Rep*. 2023;13(1):748. doi:10.1038/s41598-023-27997-3
47. Katara GK, Kulshrestha A, Mao L, et al. Mammary epithelium-specific inactivation of V-ATPase reduces stiffness of extracellular matrix and enhances metastasis of breast cancer. *Mol oncol*. 2018;12(2):208–223. doi:10.1002/1878-0261.12159
48. Erdogan B, Webb DJ. Cancer-associated fibroblasts modulate growth factor signaling and extracellular matrix remodeling to regulate tumor metastasis. *Biochem Soc Trans*. 2017;45(1):229–236. doi:10.1042/BST20160387
49. Pickup MW, Mouw JK, Weaver VM. The extracellular matrix modulates the hallmarks of cancer. *EMBO Rep*. 2014;15(12):1243–1253. doi:10.15252/embr.201439246
50. Nissen NI, Karsdal M, Willumsen N. Collagens and Cancer associated fibroblasts in the reactive stroma and its relation to Cancer biology. *J Exp Clin Cancer Res*. 2019;38(1):115. doi:10.1186/s13046-019-1110-6

51. Chitty JL, Cox TR. The extracellular matrix in cancer: from understanding to targeting. *Trends Cancer*. 2025;11(9):839–849. doi:10.1016/j.trecan.2025.05.003
52. Jacobetz MA, Chan DS, Neesse A, et al. Hyaluronan impairs vascular function and drug delivery in a mouse model of pancreatic cancer. *Gut*. 2013;62(1):112–120. doi:10.1136/gutjnl-2012-302529
53. Qin Q, Yu R, Eriksson JE, Tsai HI, Zhu H. Cancer-associated fibroblasts in pancreatic ductal adenocarcinoma therapy: challenges and opportunities. *Cancer Lett*. 2024;591:216859. doi:10.1016/j.canlet.2024.216859
54. Nishino R, Honda M, Yamashita T, et al. Identification of novel candidate tumour marker genes for intrahepatic cholangiocarcinoma. *J Hepatol*. 2008;49(2):207–216. doi:10.1016/j.jhep.2008.03.025
55. Sureshbabu A, Okajima H, Yamanaka D, et al. IGFBP-5 induces epithelial and fibroblast responses consistent with the fibrotic response. *Biochem Soc Trans*. 2009;37(Pt 4):882–885. doi:10.1042/BST0370882
56. Sirica AE. The role of cancer-associated myofibroblasts in intrahepatic cholangiocarcinoma. *Nat Rev Gastroenterol Hepatol*. 2011;9(1):44–54. doi:10.1038/nrgastro.2011.222
57. Yoshida GJ. Metabolic reprogramming: the emerging concept and associated therapeutic strategies. *J Exp Clin Cancer Res*. 2015;34:111. doi:10.1186/s13046-015-0221-y
58. Nazemi M, Rainero E. Cross-talk between the tumor microenvironment, extracellular matrix, and cell metabolism in cancer. *Front Oncol*. 2020;10:239. doi:10.3389/fonc.2020.00239
59. Li Z, Sun C, Qin Z. Metabolic reprogramming of cancer-associated fibroblasts and its effect on cancer cell reprogramming. *Theranostics*. 2021;11(17):8322–8336. doi:10.7150/thno.62378
60. Hernández-Camarero P, López-Ruiz E, Marchal JA, Perán M. Cancer: a mirrored room between tumor bulk and tumor microenvironment. *J Exp Clin Cancer Res*. 2021;40(1):217. doi:10.1186/s13046-021-02022-5
61. Butti R, Khaladkar A, Bhardwaj P, Prakasam G. Heterotypic signaling of cancer-associated fibroblasts in shaping the cancer cell drug resistance. *Cancer Drug Resist*. 2023;6(1):182–204. doi:10.20517/cdr.2022.72
62. Makinoshima H, Takita M, Matsumoto S, et al. Epidermal growth factor receptor (EGFR) signaling regulates global metabolic pathways in EGFR-mutated lung adenocarcinoma. *J Biol Chem*. 2014;289(30):20813–20823. doi:10.1074/jbc.M114.575464
63. Apicella M, Giannoni E, Fiore S, et al. Increased lactate secretion by cancer cells sustains non-cell-autonomous adaptive resistance to MET and EGFR targeted therapies. *Cell Metab*. 2018;28(6):848–865.e846. doi:10.1016/j.cmet.2018.08.006
64. Li C, Fu C, Zhou W, et al. Lactylation modification of HIF-1α enhances its stability by blocking VHL recognition. *Cell Commun Signal*. 2025;23(1):364. doi:10.1186/s12964-025-02366-x
65. Li Q, Ye C, Tian T, et al. The emerging role of ubiquitin-specific protease 20 in tumorigenesis and cancer therapeutics. *Cell Death Dis*. 2022;13(5):434. doi:10.1038/s41419-022-04853-2
66. Silakit R, Kitirat Y, Thongchot S, et al. Potential role of HIF-1-responsive microRNA210/HIF3 axis on gemcitabine resistance in cholangiocarcinoma cells. *PLoS One*. 2018;13(6):e0199827. doi:10.1371/journal.pone.0199827
67. Liu X, Ren B, Ren J, Gu M, You L, Zhao Y. The significant role of amino acid metabolic reprogramming in cancer. *Cell Commun Signal*. 2024;22(1):380. doi:10.1186/s12964-024-01760-1
68. Quintero Escobar M, Maschietto M, Krepischi ACV, Avramovic N, Tasic L. Insights into the chemical biology of childhood embryonal solid tumors by NMR-based metabolomics. *Biomolecules*. 2019;9(12):843. doi:10.3390/biom9120843
69. Hou W, Syn WK. Role of metabolism in hepatic stellate cell activation and fibrogenesis. *Front Cell Dev Biol*. 2018;6:150. doi:10.3389/fcell.2018.00150
70. Tajan M, Vousden KH. The quid pro quo of the tumor/stromal interaction. *Cell Metab*. 2016;24(5):645–646. doi:10.1016/j.cmet.2016.10.017
71. Bertero T, Oldham WM, Grasset EM, et al. Tumor-stroma mechanics coordinate amino acid availability to sustain tumor growth and malignancy. *Cell Metab*. 2019;29(1):124–140.e110. doi:10.1016/j.cmet.2018.09.012
72. Yoo HC, Yu YC, Sung Y, Han JM. Glutamine reliance in cell metabolism. *Exp Mol Med*. 2020;52(9):1496–1516. doi:10.1038/s12276-020-00504-8
73. Ko YH, Lin Z, Flomenberg N, et al. Glutamine fuels a vicious cycle of autophagy in the tumor stroma and oxidative mitochondrial metabolism in epithelial cancer cells: implications for preventing chemotherapy resistance. *Cancer Biol Ther*. 2011;12(12):1085–1097. doi:10.4161/cbt.12.12.18671
74. Wu X, Chen D, Li M, Liang G, Ye H. UCK2 promotes intrahepatic cholangiocarcinoma progression and desensitizes cisplatin treatment by PI3K/AKT/mTOR/autophagic axis. *Cell Death Discov*. 2024;10(1):375. doi:10.1038/s41420-024-02140-x
75. Li X, Zhu H, Sun W, Yang X, Nie Q, Fang X. Role of glutamine and its metabolite ammonia in crosstalk of cancer-associated fibroblasts and cancer cells. *Cancer Cell Int*. 2021;21(1):479. doi:10.1186/s12935-021-02121-5
76. Yang SM, Kim J, Lee JY, Lee JS, Lee JM. Regulation of glucose and glutamine metabolism to overcome cisplatin resistance in intrahepatic cholangiocarcinoma. *BMB Rep*. 2023;56(11):600–605. doi:10.5483/BMBRep.2023-0029
77. Yang R, Yi M, Xiang B. Novel insights on lipid metabolism alterations in drug resistance in cancer. *Front Cell Develop Biol*. 2022;10:875318. doi:10.3389/fcell.2022.875318
78. Qin J, Ye L, Wen X, et al. Fatty acids in cancer chemoresistance. *Cancer Lett*. 2023;572:216352. doi:10.1016/j.canlet.2023.216352
79. Peng S, Chen D, Cai J, et al. Enhancing cancer-associated fibroblast fatty acid catabolism within a metabolically challenging tumor microenvironment drives colon cancer peritoneal metastasis. *Mol oncol*. 2021;15(5):1391–1411. doi:10.1002/1878-0261.12917
80. Xiang X, Niu YR, Wang ZH, Ye LL, Peng WB, Zhou Q. Cancer-associated fibroblasts: vital suppressors of the immune response in the tumor microenvironment. *Cytokine Growth Factor Rev*. 2022;67:35–48. doi:10.1016/j.cytogfr.2022.07.006
81. Koppensteiner L, Mathieson L, O'Connor RA, Akram AR. Cancer associated fibroblasts - an impediment to effective anti-cancer T cell immunity. *Front Immunol*. 2022;13:887380. doi:10.3389/fimmu.2022.887380
82. Davidson S, Coles M, Thomas T, et al. Fibroblasts as immune regulators in infection, inflammation and cancer. *Nat Rev Immunol*. 2021;21(11):704–717. doi:10.1038/s41577-021-00540-z
83. Li K, Shi H, Zhang B, et al. Myeloid-derived suppressor cells as immunosuppressive regulators and therapeutic targets in cancer. *Signal Transduct Target Ther*. 2021;6(1):362. doi:10.1038/s41392-021-00670-9

84. Maggi E, Landolina N, Munari E, et al. T cells in the microenvironment of solid pediatric tumors: the case of neuroblastoma. *Front Immunol*. 2025;16:1544137. doi:10.3389/fimmu.2025.1544137
85. Lu J, Luo Y, Rao D, et al. Myeloid-derived suppressor cells in cancer: therapeutic targets to overcome tumor immune evasion. *Exp Hematol Oncol*. 2024;13(1):39.
86. Kato T, Noma K, Ohara T, et al. Cancer-associated fibroblasts affect intratumoral CD8(+) and FoxP3(+) T cells via IL6 in the tumor microenvironment. *Clin Cancer Res*. 2018;24(19):4820–4833. doi:10.1158/1078-0432.CCR-18-0205
87. Liu H, Zeng X, Ren X, et al. Targeting tumour-intrinsic N(7)-methylguanosine tRNA modification inhibits MDSC recruitment and improves anti-PD-1 efficacy. *Gut*. 2023;72(8):1555–1567. doi:10.1136/gutjnl-2022-327230
88. Konishi D, Umeda Y, Yoshida K, et al. Regulatory T cells induce a suppressive immune milieu and promote lymph node metastasis in intrahepatic cholangiocarcinoma. *Br J Cancer*. 2022;127(4):757–765. doi:10.1038/s41416-022-01838-y
89. Wang J, Loeuillard E, Gores GJ, Ilyas SI. Cholangiocarcinoma: what are the most valuable therapeutic targets - cancer-associated fibroblasts, immune cells, or beyond T cells? *Expert Opin Ther Targets*. 2021;25(10):835–845. doi:10.1080/14728222.2021.2010046
90. Ziani L, Chouaib S, Thiery J. Alteration of the antitumor immune response by cancer-associated fibroblasts. *Front Immunol*. 2018;9:414. doi:10.3389/fimmu.2018.00414
91. Deying W, Feng G, Shumei L, Hui Z, Ming L, Hongqing W. CAF-derived HGF promotes cell proliferation and drug resistance by up-regulating the c-Met/PI3K/Akt and GRP78 signalling in ovarian cancer cells. *Biosci Rep*. 2017;37(2). doi:10.1042/BSR20160470
92. Yamanaka T, Harimoto N, Yokobori T, et al. Nintedanib inhibits intrahepatic cholangiocarcinoma aggressiveness via suppression of cytokines extracted from activated cancer-associated fibroblasts. *Br J Cancer*. 2020;122(7):986–994. doi:10.1038/s41416-020-0744-7
93. Kittirat Y, Suksawat M, Thongchot S, et al. Interleukin-6-derived cancer-associated fibroblasts activate STAT3 pathway contributing to gemcitabine resistance in cholangiocarcinoma. *Front Pharmacol*. 2022;13:897368. doi:10.3389/fphar.2022.897368
94. Zhang C, Sun R, Kong B, Hu R, Du Q. Editorial: crosstalk between cancer-associated fibroblasts and tumor cells in the tumor microenvironment: an emerging target of anti-cancer immunotherapy. *Front Pharmacol*. 2023;14:1256643. doi:10.3389/fphar.2023.1256643
95. Cantallops Vilà P, Ravichandra A, Agirre Lizaso A, Perugorria MJ, Affò S. Heterogeneity, crosstalk, and targeting of cancer-associated fibroblasts in cholangiocarcinoma. *Hepatology*. 2024;79(4):941–958. doi:10.1097/HEP.0000000000000206
96. Li X, Yao QY, Liu HC, et al. Placental growth factor silencing ameliorates liver fibrosis and angiogenesis and inhibits activation of hepatic stellate cells in a murine model of chronic liver disease. *J Cell Mol Med*. 2017;21(10):2370–2385. doi:10.1111/jcmm.13158
97. Aoki S, Inoue K, Klein S, et al. Placental growth factor promotes tumour desmoplasia and treatment resistance in intrahepatic cholangiocarcinoma. *Gut*. 2022;71(1):185–193. doi:10.1136/gutjnl-2020-322493
98. Vaquero J, Lobe C, Tahraoui S, et al. The IGF2/IR/IGF1R pathway in tumor cells and myofibroblasts mediates resistance to EGFR inhibition in cholangiocarcinoma. *Clin Cancer Res*. 2018;24(17):4282–4296. doi:10.1158/1078-0432.CCR-17-3725
99. Nurmik M, Ullmann P, Rodriguez F, Haan S, Letellier E. In search of definitions: cancer-associated fibroblasts and their markers. *Int J Cancer*. 2020;146(4):895–905. doi:10.1002/ijc.32193
100. Sahai E, Astsaturov I, Cukierman E, et al. A framework for advancing our understanding of cancer-associated fibroblasts. *Nat Rev Cancer*. 2020;20(3):174–186. doi:10.1038/s41568-019-0238-1
101. Li Z, Ji X, Cong X, Gao Y, Gao J. Recent advances in nanoparticles targeting TGF-β signaling for cancer treatment. *Theranostics*. 2026;16(7):3507–3540. doi:10.7150/thno.126517
102. Östman A. PDGF receptors in tumor stroma: biological effects and associations with prognosis and response to treatment. *Adv Drug Delivery Rev*. 2017;121:117–123. doi:10.1016/j.addr.2017.09.022
103. Xu Y, Li X, Cui M, et al. Fufang-Biejia-Ruangan tablet targeting both cancer-associated fibroblasts and tumor cells by HIPPO-PI3K/AKT cascades in intrahepatic cholangiocarcinoma treatment. *Phytomedicine*. 2025;141:156690. doi:10.1016/j.phymed.2025.156690
104. Chen W, Yang A, Jia J, Popov YV, Schuppan D, You H. Lysyl Oxidase (LOX) family members: rationale and their potential as therapeutic targets for liver fibrosis. *Hepatology*. 2020;72(2):729–741. doi:10.1002/hep.31236
105. Gross MI, Demo SD, Dennison JB, et al. Antitumor activity of the glutaminase inhibitor CB-839 in triple-negative breast cancer. *Mol Cancer Ther*. 2014;13(4):890–901. doi:10.1158/1535-7163.MCT-13-0870
106. Zhu G, Guan F, Li S, et al. Glutaminase potentiates the glycolysis in esophageal squamous cell carcinoma by interacting with PDK1. *Mol Carcinog*. 2024;63(5):897–911. doi:10.1002/mc.23696
107. Boudreau A, Purkey HE, Hitz A, et al. Metabolic plasticity underpins innate and acquired resistance to LDHA inhibition. *Nat Chem Biol*. 2016;12(10):779–786. doi:10.1038/nchembio.2143
108. Noble RA, Bell N, Blair H, et al. Inhibition of monocarboxyate transporter 1 by AZD3965 as a novel therapeutic approach for diffuse large B-cell lymphoma and Burkitt lymphoma. *Haematologica*. 2017;102(7):1247–1257. doi:10.3324/haematol.2016.163030
109. Batra H, Pawar S, Bahl D. Curcumin in combination with anti-cancer drugs: a nanomedicine review. *Pharmacol Res*. 2019;139:91–105. doi:10.1016/j.phrs.2018.11.005
110. Thongpon P, Intuyod K, Chomwong S, et al. Curcumin synergistically enhances the efficacy of gemcitabine against gemcitabine-resistant cholangiocarcinoma via the targeting LAT2/glutamine pathway. *Sci Rep*. 2024;14(1):16059. doi:10.1038/s41598-024-66945-7
111. Cui Q, Josephraj S, Gu B, Liu JY, Zhang JT. Targeting fatty acid synthase for cancer drug discovery: retrospective analyses and outlook. *Pharmacol Rev*. 2026;78(1):100105. doi:10.1016/j.pharmr.2025.100105
112. Biffi G, Tuveson DA. Diversity and biology of cancer-associated fibroblasts. *Physiol Rev*. 2021;101(1):147–176. doi:10.1152/physrev.00048.2019
113. Xiang Q, Chen W, Ren M, et al. Cabozantinib suppresses tumor growth and metastasis in hepatocellular carcinoma by a dual blockade of VEGFR2 and MET. *Clin Cancer Res*. 2014;20(11):2959–2970. doi:10.1158/1078-0432.CCR-13-2620
114. Thongchot S, Ferraresi A, Vidoni C, et al. Resveratrol interrupts the pro-invasive communication between cancer associated fibroblasts and cholangiocarcinoma cells. *Cancer Lett*. 2018;430:160–171. doi:10.1016/j.canlet.2018.05.031
115. Singh S, Srivastava SK, Bhardwaj A, Owen LB, Singh AP. CXCL12-CXCR4 signalling axis confers gemcitabine resistance to pancreatic cancer cells: a novel target for therapy. *Br J Cancer*. 2010;103(11):1671–1679. doi:10.1038/sj.bjc.6605968
116. Fang Z, Meng Q, Xu J, et al. Signaling pathways in cancer-associated fibroblasts: recent advances and future perspectives. *Cancer Commun*. 2023;43(1):3–41. doi:10.1002/cac2.12392

117. Mas-Moruno C, Rechenmacher F, Kessler H. Cilengitide: the first anti-angiogenic small molecule drug candidate design, synthesis and clinical evaluation. *Anticancer Agents Med Chem*. 2010;10(10):753–768. doi:10.2174/187152010794728639
118. Jiang H, Hegde S, Knolhoff BL, et al. Targeting focal adhesion kinase renders pancreatic cancers responsive to checkpoint immunotherapy. *Nature Med*. 2016;22(8):851–860. doi:10.1038/nm.4123
119. Li L, Zhou Y, Zhang Y, Hu H, Mao HQ, Selaru FM. A combination therapy of bortezomib, CXCR4 inhibitor, and checkpoint inhibitor is effective in cholangiocarcinoma in vivo. *iScience*. 2023;26(3):106095. doi:10.1016/j.isci.2023.106095