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Piezo1: the Potential Novel Target for Radiation-induced Liver Fibrosis by Regulating FAP + fibroblasts

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Abstract

Radiation-induced liver fibrosis is a serious complication of radiotherapy in patients with liver cancer and is characterized by excessive deposition of the extracellular matrix (ECM). The activation of cancer-associated fibroblasts (CAFs) is central to this event. Piezo1 is a mechanoreceptor that is highly expressed in liver tissue and is closely related to the fibrotic process. CAFs are highly heterogeneous, and different cell populations perform different functions. Recent studies have shown that fap, an important surface marker of the CAF membrane, presumably plays a "hub" role upstream of α-smooth muscle actin (α-SMA). This article reviews the unique microenvironment of liver cancer and liver fibrosis and the role of piezo1 and CAFs in liver fibrosis. Building upon the foundational evidence, we formulate a hypothesis that radiation-induced ECM remodeling activates Piezo1-mediated mechanotransduction, driving HIF-1α/TGF-β pathways to stimulate CAF activation (manifested by FAP upregulation), which may synergistically aggravate liver fibrosis and hepatocarcinogenesis.

Graphical abstract

This illustration depicts a malignant cycle within the tumor microenvironment of hepatocellular carcinoma and radiation-induced liver fibrosis. Ionizing radiation activates the mechanosensitive ion channel Piezo1, which mediates macrophage polarization and regulates two key subpopulations of cancer-associated fibroblasts, specifically FAP+ CAFs and α-SMA+ CAFs. This process exacerbates extracellular matrix remodeling and promotes liver fibrosis.

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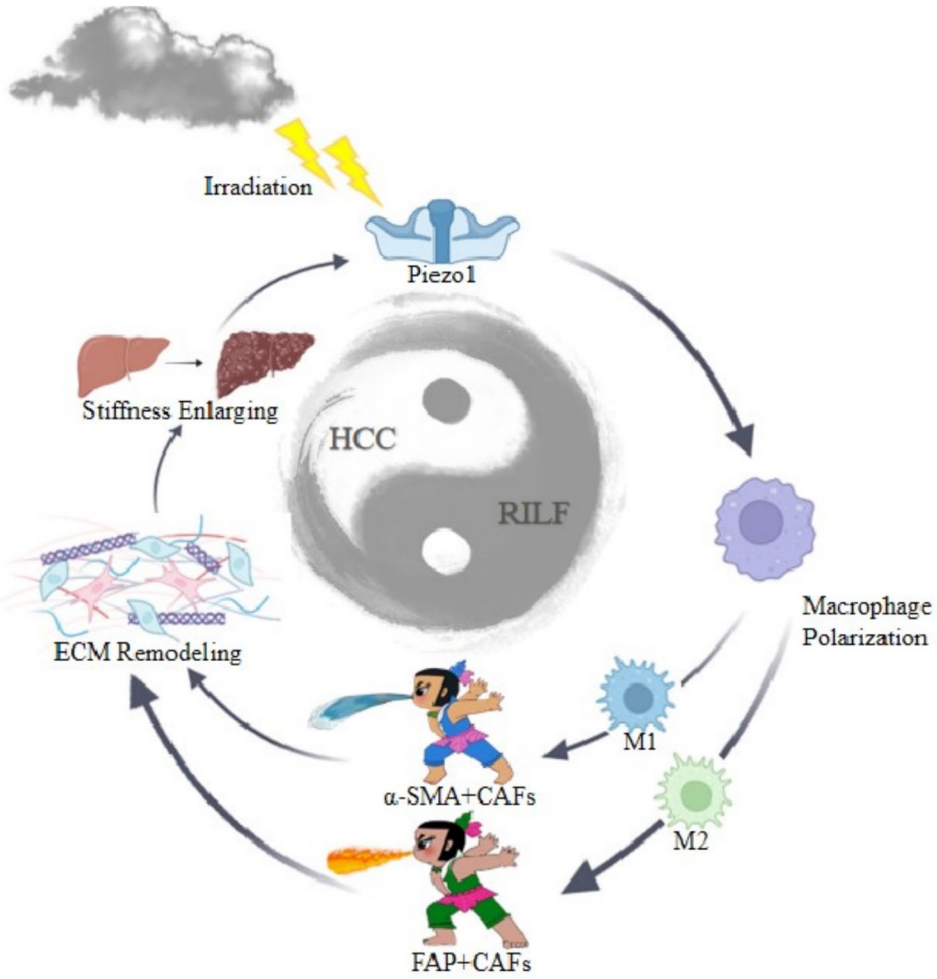

Keywords Liver fibrosis · Piezo 1 · Cancer-associated fibroblasts · FAP · Macrophage polarization

Abbreviations

ECM	Extracellular matrix
CAFs	Cancer-associated fibroblasts
α-SMA	α-Smooth muscle actin
FAP	Fibroblast activation protein
HIF-1a	Hypoxia inducible factor 1
TGF-β	Transforming growth factor-β
HCC	Hepatocellular carcinoma
MMPs	Matrix metalloproteinases
TIMPs	Tissue inhibitors of metalloproteinases
HGF	Hepatocyte growth factor
PDGFR-β	Platelet derived growth factor receptor beta
CCL4	Carbon tetrachloride
BML	Benign metastasizing leiomyoma
RILF	Radiation-induced liver fibrosis
TME	Tumor microenvironment
TAMs	Tumor-associated macrophages
AP1	Activating protein-1
EDN1	Endothelin-1
CSF-1	Colony-stimulating factor 1
ICIs	Immune checkpoint inhibitors
RT	Radiation therapy
BMDCs	Bone marrow-derived macrophages
EMT	Epithelial mesenchymal transition
EndMT	Endothelial−mesenchymal transition
ILGF II	Insulin-like growth factor II
myCAFs	Myofibroblast CAFs
iCAFs	Inflammatory CAFs
apCAFs	Antigen-presenting CAFs
TIME	Tumor immune microenvironment
pCAFs	Tumor-promoting CAFs
PD-L1	Programmed cell death 1 ligand 1
CTGF	Connective tissue growth factor
STAT6	Signal transducer and activator of transcription 6
TLR4	Toll-like receptor 4

BMDMs	Bone marrow-derived macrophages
ROS	Reactive oxygen species
FN	Fibronectin
CTSS	Cathepsin S
MAPK	Mitogen-activated protein kinase

Introduction

Chronic liver injury causes liver inflammation and even fibrosis. Liver fibrosis is a complex end-stage progression, which is process that involves not only complex processes of cell crosstalk and cytokine interaction in the liver microenvironment but also the common pathophysiological changes in clinical diseases such as cirrhosis and hepatocellular carcinoma (HCC) [1]. The main pathological changes associated with liver fibrosis are an abnormal increase in ECM synthesis and an abnormal deficiency of degradation, of which the activation of fibroblasts into myofibroblasts is the critical link [2].

After certain stimulation, fibroblasts transform into myofibroblasts, which can secrete α-SMA and collagen, the key components of the ECM [3]. They also produce matrix metalloproteinases (MMPs) and tissue inhibitors of metalloproteinases (TIMPs), which play important roles in ECM remodeling [4]. Myofibroblasts can also express FAP, hepatocyte growth factor (HGF), platelet derived growth factor receptor beta (PDGFR-β) and IGFRII to participate in the occurrence and progression of hepatocellular carcinoma [5]. The origin of myofibroblasts is believed to include hepatic stellate cells, endothelial cells, and fibroblasts [5]. Beyond that, immune cells such as macrophages and T cells also participate in regulating fibrosis and carcinoma proliferation [4, 6–9].

At present, most liver fibrosis reported in the literature is induced by carbon tetrachloride (CCL4) or benign metastasizing leiomyoma(BML) surgery, however, as radiotherapy has already become an important treatment for HCC, especially for stage III patients, radiation-induced liver fibrosis (RILF) has also attracted attention [10, 11]. Ionizing radiation can induce the activation of myofibroblasts, releasing a series of growth factors and cytokines that drive ECM deposition, matrix stiffness, and changes in the tumor microenvironment (TME), which further induce the activation of CAFs, thus resulting in positive feedback [12]. Multiple signal transduction pathways are involved and eventually lead to irreversible fibrosis [13]. Clinically, such chronic changes are mostly the adverse consequences of radiotherapy for malignant liver tumors, which not only damage the tissues around the tumor but also greatly reduce the radiotherapy efficacy of the tumor [14].

Emerging evidence underscores RILF as a distinct pathological entity within hepatocellular carcinoma management [14]. Unlike conventional chemical-induced fibrosis models, RILF is characterized by biomechanical reprogramming of the tumor microenvironment, where ionizing radiation initiates self-perpetuating cycles of ECM stiffening and CAF activation [15, 16]. Mechanosensitive ion channel Piezo1 is central to this process, converting radiation-induced mechanical stimuli into biochemical signals through HIF-1α/TGF-β signaling pathways. This process subsequently drives the differentiation of FAP + CAFs and pathological remodeling of the ECM [17, 18]. This mechanobiological paradigm not only redefines our understanding of fibrogenic progression post-radiotherapy but also positions Piezo1 as a promising therapeutic node for disrupting the fibrosis-cancer axis. Elucidating the spatiotemporal dynamics of Piezo1-mediated mechanotransduction in RILF may unveil novel strategies to mitigate radiotherapy complications while preserving oncological efficacy.

Microenvironment of liver fibrosis

RILF represents a serious complication following radiotherapy for abdominal and thoracic malignancies [19, 20]. As a global health challenge, HCC arises within a unique TME triad encompassing chronic inflammation, fibrosis, and carcinogenesis. While HCC predominantly develops against a backdrop of chronic liver injury and fibrosis [21], the role of fibrosis remains controversial due to its "double-edged sword" nature: it serves as a compensatory repair mechanism yet paradoxically fosters malignant transformation through microenvironmental remodeling [22]. This duality likely stems from stage-dependent fibrotic responses, etiological variations (e.g., viral, alcoholic, or metabolic origins), and crosstalk with oncogenic pathways [23, 24].

Within this fibrotic TME, ECM dynamics are orchestrated through multifaceted interactions involving hepatic stellate cells (HSCs), immune populations, and stromal components. Activated HSCs undergo phenotypic conversion into CAFs—central architects of ECM pathology—which drive excessive matrix deposition via pro-fibrotic factors (α-SMA, FAP, COL1A1.etc.) [15]. This transition is mechanistically governed by biomechanical stimuli, metabolic adaptation, and reciprocal immune interactions [25–27]. For instance, CAF-derived CCL2 and TGF-β polarize macrophages toward pro-fibrotic M2 phenotypes, while M2 macrophages reciprocally amplify HSC activation, creating a self-reinforcing fibrogenic loop [28–31].

Sclerotic liver tissue, characterized by aberrant ECM accumulation, constitutes a hallmark of both advanced fibrosis and HCC [15]. The evolving matrix composition

and rigidity directly modulate tumor behavior, with stiffened ECM activating mechanosensitive pathways (YAP/TAZ) to promote malignant phenotypes [16]. Such biomechanical perturbations, coupled with biochemical alterations in collagen cross-linking and growth factor sequestration, collectively rewire the TME to favor tumor progression.

In this special microenvironment, macrophages, which can be divided into M1-polarized and M2-polarized phenotypes according to their polarization state and biological function [32], play an indispensable role in tumor growth, proliferation, metastasis, and immune escape. Tumor-associated macrophages (TAMs) exhibit the M1 phenotype in the early stages of tumorigenesis, whereas the M2 phenotype shows progresses as the tumor progresses, expressing immune inhibition in the TME and promoting malignant progression [33]. Recent studies have shown that the behavior of TAMs is regulated by changes in the stiffness of the ECM in HCC, which often predicts a poor prognosis [34]. ECM stiffening-mediated mechanical stimulation activates mechanosensors, such as piezo1 ion channels, on the membranes of tumor and stromal cells [35].

Piezo1, a cation channel protein located on the cell membrane, has a highly sensitive mechanosensing ability [36]. Matrix stiffness regulates macrophage polarization through piezo1. As shown in Fig. 1, after the mechanical stimulation of the macrophage membrane by piezo1, a large number of influxes of calcium ions combine with F-actin; on the one hand, activating protein-1(AP1) is activated, and HIF-1a is stabilized through endothelin-1 (EDN1), which is expressed by piezo1, to upregulate the expression of inflammatory factors. On the other hand, it also activated the NF-κB inflammatory signaling pathway. In this way, the polarization of macrophages to the M1 phenotype was achieved [37, 38]. The energy supply required for this process is also achieved by enhancing the aerobic glycolysis of macrophages via the piezo1/Ca2 + /HIF-1a axis [39]. In different microenvironments, macrophages that sense mechanical signals can also polarize toward the M2 phenotype by activating TGF-β and expressing colony-stimulating factor 1 (CSF-1), which can promote macrophage recruitment [40].

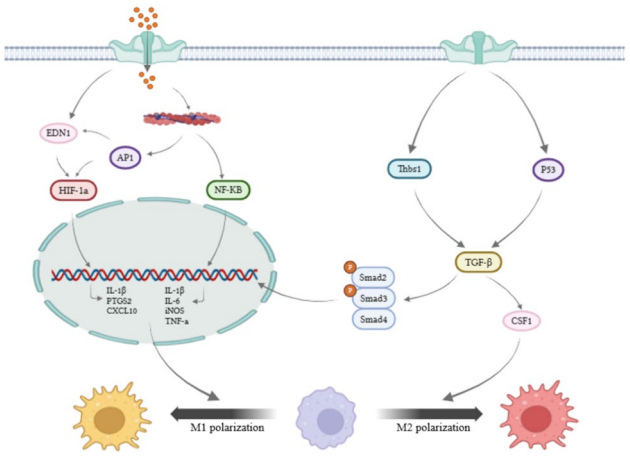

Fig. 1 Pathways about how piezo1 regulates macrophage polarization (Created with BioRender.com)

The functional expression of macrophages after irradiation may differ across various tissues and periods [41, 42]. In the early stage of tumors, macrophages differentiate into proinflammatory types and help kill tumor cells. However, in the later stage, resident and recruited macrophages are more likely to promote angiogenesis and tissue repair, gradually leading to scar fibrosis, aggravated tissue fibrosis, tumor regeneration, metastasis and recurrence [43]. TAMs are closely related to tumor development because of their powerful proangiogenic effects and ability to support tumor cell survival, so the high density of TAMs in the TME also implies a poor prognosis [44].

In addition, in the process of tumor development, different subsets of the two phenotypes of macrophages can be transformed into each other [45], and targeted reprogramming of TAMs for tumor immunotherapy of HCC has recently become a recent research focal issue. For the past few decades, targeted combination immunotherapy has been the treatment of choice for inoperable advanced liver cancer. However, in recent years, the advent of immune checkpoint inhibitors (ICIs) has provided a new idea for the treatment of HCC.

Fortunately, a large number of studies and clinical trials have confirmed the feasibility of this treatment. Studies by Cheng et al. and Chen et al. confirmed that inhibiting or reversing M2-type polarized macrophages can effectively reshape the HCC TME and ultimately enhance the antitumor effect [46, 47] Liu et al. reported that blocking macrophages in the tumor immune barrier can improve the effect of ICIs and improve the anti-tumor efficiency [48]. Reversal of M2-TAMs may be achieved by down-regulating glycolysis levels, silencing the Wnt2b/β-catenin/c-myc pathway, or inhibiting the PI3k/PKB pathway [49, 50]. Although the introduction of radiotherapy as an effective treatment for most solid tumors for the treatment of HCC is obviously backward and there is no clear consensus on the optimal timing of intervention, existing studies have shown that the combination of ICI and radiation therapy (RT) can not only reshape the local TME but also reduce the immunosuppressive effect induced by RT and enhance the distant effect of radiation. The synergy between ICIs and RT may be an important direction for future development [51–53].

Cancer-associated fibroblasts

The TME plays a crucial role in promoting the progression of fibrosis and organizing malignant behavior [54]. A variety of cells and complex components constitute the TME

[55]. When stimulated with stimuli such as inflammation or mechanical forces, cells such as fibroblasts are activated into CAFs. CAFs are the main component of the liver TME [56] and not only regulate the remodeling and degradation of the ECM but also regulate the immune microenvironment of tumors through crosstalk with cells in the TME [57]. The niches of intrahepatic malignancy and fibrosis receive accelerated positive feedback.

CAF heterogeneity and functional plasticity: from ECM remodeling to tumor stroma crosstalk

CAFs are considered to be derived from various cell types, including fibroblasts, bone marrow-derived macrophages (BMDCs), epithelial cells undergoing epithelial mesenchymal transition (EMT), endothelial cells undergoing endothelial−mesenchymal transition (EndMT), adipocytes and hepatic stellate cells [58]. In the liver TME, CAFs express markers like α-SMA, type I collagen, FAP, and PDGFR-β to regulate tumor growth and survival [59] Table 1 categorizes CAF subtypes based on their cellular origins, functional roles and key signaling pathways. CAFs exhibit significant plasticity and phenotypic heterogeneity [60], with three main subgroups: myofibroblast CAFs (myCAFs) which remodel the ECM, inflammatory CAFs (iCAFs), and antigen-presenting CAFs (apCAFs) which support the tumor niche [61, 62].

CAFs demonstrate functional heterogeneity in the tumor microenvironment, broadly categorized into pro-tumorigenic (pCAFs) and restrictive (rCAFs) subtypes [82, 83]. pCAFs, mainly characterized by elevated expression of FAP-α and α-SMA, drive malignant progression by secreting immunosuppressive factors (e.g., TGF-β, IL-6, CXCL12) to impair anti-tumor immunity and directly enhance cancer cell proliferation, invasion, and metastasis [84, 85]. These cells dominate the CAF population in most solid tumors. In contrast, rCAFs counteract tumorigenesis through distinct mechanisms: meflin-expressing subsets in pancreatic cancer modulate tumor stemness, while BMP-4-secreting myofibroblasts in oral carcinomas suppress cancer cell stemness [80]. Furthermore, rCAFs restrict tumor dissemination via physical barrier formation or immunostimulatory microenvironment remodeling, as observed in colorectal and bladder cancers [80, 86]. Despite their therapeutic relevance, the identification of definitive surface markers for rCAFs remains challenging, hindering targeted intervention strategies.

Notably, CAFs plasticity critically influence tumor evolution. Under biomechanical and biochemical stimuli such as matrix stiffening, hypoxia, or TGF-β signaling, rCAFs undergo phenotypic switching toward pCAFs [85, 87]. This phenotypic plasticity, however, appears to be contingent upon dynamic alterations within the TME. The bidirectional conversion between myCAFs and iCAFs has been documented in pancreatic cancer models [61]. Supporting this concept, single-cell transcriptomic analyses by Wu et al. [88] revealed a transcriptional continuum among CAF subpopulations, providing indirect evidence for their functional reversibility. Nevertheless, critical gaps persist in mechanistic validation—notably the absence of direct experimental evidence from lineage-tracing studies or controlled in vitro induction systems. These unresolved questions highlight the

Table 1 Summary of actual and potential features of different subtypes of CAFs

Marker	Potential cellular origin	Key functions	Signaling pathways	References
FAP	Activated fibroblasts, tumor stroma	ECM remodeling (MMP secretion); Immuno`ression (CD8 + T cell inhibition); Tumor invasion/metastasis promotion	TGF-β/Smad Wnt/β-catenin	[17, 18, 63–66]
α-SMA	Myofibroblasts, activated fibroblasts	Matrix contractility enhancement; Fibrotic barrier formation; Angiogenesis promotion	RhoA/Rock1 YAP/TAZ	[67–71]
PDGFR	Mesenchymal stem cells, pericytes	Fibroblast proliferation; Radiation-induced fibrosis; Synergistic CAF activation with TGF-β	PI3K/Akt MAPK/ERK	[72–74]
FSP1	EMT-derived fibroblasts, circulating fibroblasts	Tumor cell migration; T cell infiltration suppression; Chemotherapy resistance mediation	JAK2/STAT3	[75, 76]
IGF- II	HSCs, metabolic CAFs	Metabolic support; Cancer stem cell maintenance; OXPHOS activation	IGF1R/PI3K/Akt IGF1R/c-JUN	[77–79]
Meflin	PSCs	Tumor Suppression; Anti-fibrotic activity; Cytotoxic T cell infiltration enhancement; Mechanical homeostasis maintenance	Wnt/R-spondin SHH/SMO	[80, 81]

Summary of actual and potential features of different subtypes of CAFs.

FAP fibroblast activation protein, *ECM* extracellular matrix, *MMP* matrix metalloproteinase, *α-SMA* α-smooth muscle actin, *PDGFR* Platelet derived growth factor receptor, *FSP1* fibroblast-Specific Protein 1, *EMT* epithelial mesenchymal transition, *IGF- II* insulin-like growth factor II, *HSC* hepatic stellate cell, *CAF* cancer-associated fibroblast, *OXPHOS* oxidative phosphorylation, *PSC* pancreatic stellate cells, *SHH* sonic Hedgehog, *SMO* smoothened

need for future investigations employing spatial–temporal resolution techniques to delineate CAF plasticity dynamics. Elucidating the molecular determinants governing the rCAF-to-pCAF phenotypic shift may yield pivotal insights into reprogramming immunosuppressive tumor ecosystems, thereby uncovering actionable therapeutic vulnerabilities to reinvigorate anti-tumor immunity.

Key CAF markers include α-SMA and FAP. Depletion of α-SMA + CAFs leads to poor tumor differentiation and accelerated tumor progression, while depletion of FAP + CAFs enhances antitumor immunity and improves responses to PD-L1 inhibitors [89]. FAP + CAFs contribute to immune suppression and evasion via CXCL12, making them a target for immunotherapy [18, 65], which is also consistent with the results observed in clinical trials [90]. In addition, CAFs can also express HGF, promoting EMT and chemotherapy resistance in tumor cells [91].

FAP + CAFs: orchestrators of fibrotic niche remodeling and tumor stroma crosstalk in HCC

FAP is a serine protease that digests and breaks down collagen. Hepatic fibrosis is known to result from an imbalance between ECM accumulation and degradation in the TME [92]. ECM remodeling adjusts the structure of the TME and promotes the formation of tumor blood vessels. By expressing FAP, pericytes stabilize blood vessels in tumor tissues [93]. In addition, the enzymatic activity of FAP can regulate the existence, recruitment, proliferation and differentiation of CAFs [94] to achieve positive feedback self-protection. In addition to being present in CAFs and pericytes, FAP has also been identified in various cancer cells [95–97]. Hypoxia in tumor tissue can effectively induce CAFs to express FAP and promote the malignant behavior of tumors [98].

FAPs are thought to be rarely expressed in healthy liver tissue but are significantly expressed in the fibrotic liver and desmoplastic stroma of HCC [99, 100]. In particular, in a hypoxic environment, the FAP expression level is positively correlated with HIF-1a, and Snail expression is also upregulated [101]. These findings suggest that high expression of FAP is closely related to the EMT process in HCC, the degree of tumor vascular invasion, and the poor prognosis of HCC patients. It has been confirmed that FAP expression is positively correlated with the severity of liver fibrosis [99, 102, 103]. Moreover, FAP inhibition reduces collagen in the liver and α-SMA + CAFs, leading to ECM remodeling [99]. In addition, FAP removal can redouble the proliferation of normal hepatocytes and regulate liver regeneration, which may be related to the ability of FAP + CAFs to express and promote HGF release [104]. Nevertheless, FAP + CAFs in HCC enhance macrophage infiltration and M2 polarization and express HGF to activate the Met pathway to promote tumor metastasis and invasion and mediate chemotherapy resistance [105–107]. Therefore, high FAP expression is considered an independent predictor of poor overall survival, and elimination of FAP + CAFs is an effective scheme for reducing liver fibrosis and inhibiting HCC cell proliferation, invasion, and metastasis.

Interestingly, the expression of FAP and α-SMA in cells seems to differ. α-SMA + CAFs exist in the fibrotic mature ECM region, mediate cell contraction and regulate ECM crosslinking, whereas FAP + CAFs are usually active in collagen-rich fibrous septa and express higher levels of MMPs and tissue plasminogen activator to achieve a synthetic and proteolytic ECM phenotype [104, 108, 109]. Diana et al. used polyacrylamide hydrogels with different stiffnesses to simulate ECMs with different matrix stiffnesses and reported that the expression of fap and α-SMA showed opposite trends, indicating a gradual phenotypic transition of the fap^{hi} but an $\alpha\text{-SMA}^{low}$ fibroblast subpopulation to the fap^{low} but an $\alpha\text{-SMA}^{hi}$ fibroblast subpopulation as the stiffness changed from small to large. Overall, we hypothesize that the unique heterogeneity of CAFs may result from spatiotemporal dynamic changes in ECM composition and elasticity in fibrosis and cancer and that the expression of FAP and α-SMA occurs sequentially in fibrotic livers at different stages in a stiffness-dependent manner. Targeting different markers of CAFs may offer clinical possibilities for differentially regulating inflammation and ameliorating fibrosis.

Additionally, FAP + CAFs can also express small amounts of connective tissue growth factor (CTGF) and PDGF to regulate the fibrosis process [104], and M2 macrophages secrete matrix metallopeptidase 12(MMP12) via fibrolysis through the activation and phosphorylation of signal transducer and activator of transcription 6(STAT6) mediated by IL-4 and IL-13 [61], which provides strong evidence that FAP + CAFs regulate the dissolution of the ECM. Indeed, the exact overlap between the FAP + and α-SMA + CAF subsets has been revealed [109], but it remains undiscovered whether FAP + and α-SMA + are simply two overlapping distinct cell subsets, whether there is a temporal or spatially dependent transition between them, and whether there is a regulatory relationship between these two subsets. These issues require further experimental investigation.

A latest study revealed a correlation between FAP + CAFs and ionizing radiation [110]: electron irradiation leads to a marked increase in FAP expression and the proliferation of FAP + CAFs, as well as the significant development of radiation resistance. In other words, when malignant tumors undergo radiotherapy, while long-term ionizing radiation effectively kills tumor cells, it may also result in high FAP expression, thereby not only amplifying the protumor effects of FAP + CAFs but also impeding the efficacy of radiotherapy. Consequently, targeting FAP + represents a crucial therapeutic strategy.

Targeting Piezo1 in radiation fibrosis: from mechanosensing to therapy

Piezo1-driven mechanosignaling in fibrotic reprogramming

Cells can sense tiny alterations in the microenvironment [111]. While multiple factors underlie inflammatory processes, damaging mechanical stimuli have been identified as significant contributors to both acute and chronic inflammatory pathogenesis [112–114]. Piezo1 is a mechanosensitive ion channel, which can sense mechanical stress to cause inflammation or participate in the progression of inflammation [115]. The stiffness of the liver increases with fibrosis, and matrix stiffness is often used as an index to evaluate tissue stiffness [116]. Matrix stiffness regulates macrophage polarization via mechanoreceptors. When macrophages are mechanically stimulated, they first induce the activation of AP-1 through piezo1, promote the expression of endothelin-1 and the stability of HIF1α, and then upregulate the expression of inflammatory cytokines (such as IL-1β, PTGS2, and CXCL10) [37]. Additionally, piezo1 can activate signaling pathways such as the NF-KB and Toll-like receptor 4(TLR4) pathways, which regulate macrophage polarization and phagocytic activity [38, 117].

Interestingly, piezo1 not only modulates the proinflammatory M1 phenotype of macrophages but also increases the M2-type polarization of TAMs in the TME [118]. Chen et al. used hydrogels and reported that different substrate stiffnesses also affect the phenotypic changes of macrophages [118]. Bone marrow-derived macrophages (BMDMs) cultured in vitro on soft hydrogels expressed more ROS, IL-1β, and TNF-α, while they secreted more IL-4 and TGF-β on hard hydrogels, with little reactive oxygen species (ROS) expression. The activation of CAFs with different subsets, such as FAP and α-SMA, leads to the remodeling of the ECM, and the imbalance between their deposition and degradation leads to an increase in matrix stiffness in the TME. Changes in hardness further regulate macrophage infiltration, recruitment, and polarization through piezo1 and ultimately promote the adverse development of fibrosis and tumor invasion and metastasis [119]. CAFs and TAMs are highly positively correlated in advanced tumors, and the expression of their markers jointly predicts their prognosis [120]. Cytokines (such as CCL2, IL-8, IL-10, and TGF-β) secreted by CAFs can also promote the recruitment of monocytes and their transformation into M2-TAMs [121]. The above process may be achieved by the influx of $Ca2+$ from piezo1 after mechanical stimulation through the TGF-β signaling pathway [122]. Therefore, targeting the different signaling pathways mediated by piezo1 can not only regulate the polarization of macrophages to different phenotypes but also effectively reduce the activation of CAFs, which may constitute a new strategy for the treatment of liver fibrosis and HCC [123].

Prior experimental studies have indicated that irradiation directly upregulates the expression of the piezo1 protein, both in animal and in vitro experiments [124]. Researchers have also reported that piezo1 enhances the phagocytosis of TAMs, resulting in a marked increase in M2 polarization compared with M1 polarization. High expression of piezo1 was also observed in M2 TAMs. These findings suggest that during the radiotherapy of malignant tumors, piezo1 establishes a positive feedback loop with M2 TAMs. Another report confirmed the positive correlation between IR and piezo1, revealing significant upregulation of surface markers in CAFs [125].

Piezo1-Dependent signaling networks in RILF

Macrophages can sense abnormal mechanical signals in liver fibrosis and play a crucial role in the progression of fibrosis. Myeloid-specific piezo1 promotes the activation of CAFs by regulating macrophage infiltration, polarization, and inflammation and ultimately causes liver fibrosis [126]. The process of RILF is roughly the same as that of liver fibrosis in general, in which the key initiating factor is the activation of CAFs. CAF activation mediated by TGF-β/Smad signaling is a key step in radiation-induced liver injury and fibrosis. Piezo1 is a mechanosensitive cation channel that has been found to play an important role in liver fibrosis induced by CCL4 and BML surgery [126]. Huang et al. reported that piezo1 can regulate radiation-induced EMT via positive feedback with TGF-β1, accompanied by increased expression of α-SMA, fibronectin and vimentin [125]. Taken together, these findings suggest that piezo1 plays a vital role in RILF.

Prolonged exposure to ionizing radiation can trigger the progression of chronic inflammation into severe fibrosis [127]. At present, the TGF-β/Smad signaling pathway is considered to be the most important pathway in radiation-induced organ fibrosis and upregulates the expression of α-SMA and FAP downstream [128]. In RILF, not only is TGF-β/Smad significantly activated but also Smad7 expression is inhibited, leading to increased EMT and CAF activation [129–131]. In addition, lipoxin A4 (LXA4) produced by arachidonic acid has been confirmed to reverse tissue fibrosis by targeting the TGF-β/Smad pathway and downregulating pro-fibrotic cytokines [132]. Ionizing radiation can also upregulate the expression of the LXA4 receptor through crosstalk with the TGF-β/Smad signaling pathway during fibrosis [133].

HIF-1α is also known to be an important regulator of TGF-β signaling and to reduce radiation-induced ROS

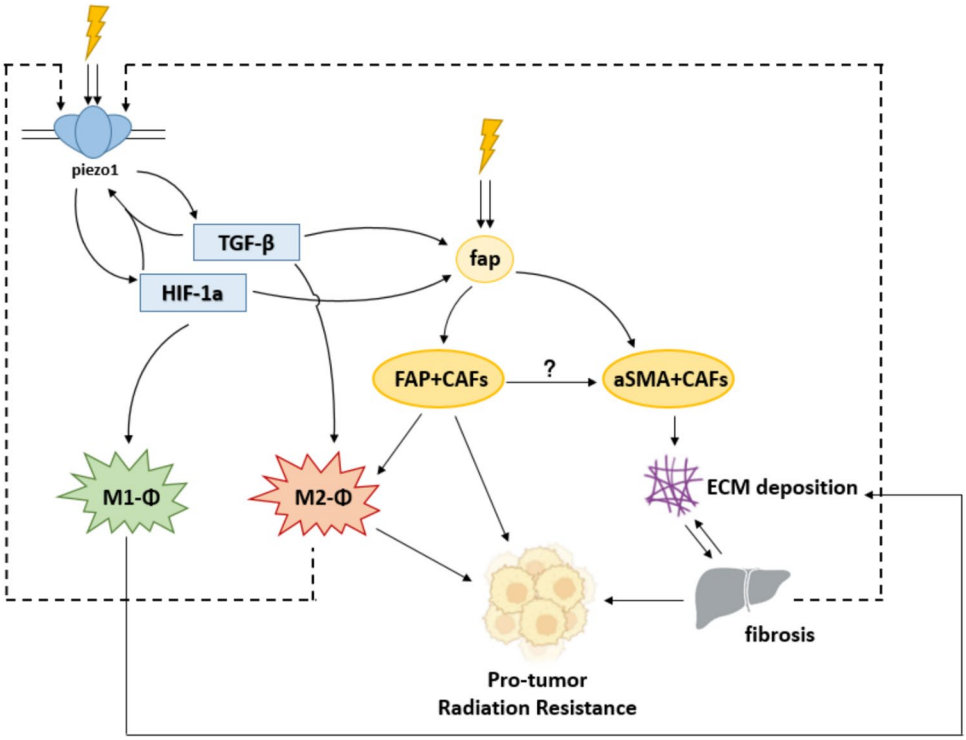

Fig. 2 Regulation mechanism of piezo1 in RILF (Created with BioRender.com)

generation to reduce the number of damaging factors in activated CAFs. It has been reported that HIF-1 and calcium signaling interact to regulate the progression and metastasis of malignant tumors in the context of cancer [134]. As mentioned earlier, ionizing radiation increases the expression of piezo1, a mechanosensitive ion channel, and increases Ca2 + influx in the activated state. When the plasma membrane is exposed to ionizing radiation, as shown in Fig. 2, the synergistic effect between the Ca2 + /HIF-1α pathway and the TGF-β1/Smad signal transduction pathway is facilitated by the "switch" on the plasma membrane, which eventually leads to the occurrence and aggravation of fibrosis [135].

The radiation-induced inflammatory response is also an important mechanism of tissue damage, and CAFs are particularly essential in this process. As mentioned above, piezo1 is upregulated in response to changes in ECM stiffness due to ECM deposition caused by myofibroblast activation, which regulates the polarization of TAMs and promotes the aggravation of fibrosis and tumor invasion. Radiation can increase the expression of FAP, α-SMA, fibronectin (FN), CTGF and other proteins in response to the occurrence of liver fibrosis. In addition, recent reports have revealed that macrophage-derived cathepsin S (CTSS) can promote liver fibrosis through ECM remodeling [136]. However, by knocking out piezo1 in macrophages from fibrotic samples, researchers have shown that not only are M1-type macrophages reduced but also EMT and ECM deposition are downregulated, and Ca2 + -dependent CTSS secretion is also inhibited [126]. These findings suggest that piezo1 not only regulates macrophage polarization and the inflammatory response but also promotes liver fibrosis by regulating CTSS secretion. Although its role in liver fibrosis has been well established, its regulatory role in RILF has not been demonstrated and needs to be explored.

Conclusion

RILF remains a formidable complication in hepatocellular carcinoma radiotherapy, with mechanosensitive FAP + CAFs emerging as pivotal pathological effectors. Central to this process, ionizing radiation triggers extracellular matrix stiffening that activates Piezo1—the biomechanical transducer coordinating two cardinal pathways: (1) HIF-1α/TGF-β signaling driving FAP + /α-SMA + CAF activation and excessive ECM deposition; (2) macrophage mechanopolarization sustaining pro-fibrotic niches. This vicious cycle establishes Piezo1 as the master regulator of FAP + CAF expansion in RILF, wherein mechanical stimuli are transduced into biochemical signals that perpetuate fibrocarcinogenesis.

Targeting Piezo1 represents a strategic approach to disrupt FAP + CAF pathogenicity. Pharmacological inhibition attenuates FAP expression by blocking HIF-1α/TGF-β signaling, while nanoparticle-mediated Piezo1 silencing could mechanically reprogram CAFs toward quiescent states. Notably, FAP itself may serve dual roles: as both a biomarker of Piezo1-driven CAF activation and a therapeutic

vulnerability for radiation fibrosis mitigation. Future investigations should prioritize spatiotemporally mapping Piezo1 activation patterns during RILF progression, developing tissue-selective mechanotherapeutics, and exploring combinatorial strategies that concurrently address biomechanical and immunological drivers of fibrocarcinogenesis.

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Declarations

Competing interests The authors declare no competing interests.

Ethical approval Not applicable.

Consent to participate Not applicable.

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References

1. Li H (2022) Intercellular crosstalk of liver sinusoidal endothelial cells in liver fibrosis, cirrhosis and hepatocellular carcinoma. Dig Liver Dis 54(5):598–613
2. Kisseleva T, Brenner D (2021) Molecular and cellular mechanisms of liver fibrosis and its regression. Nat Rev Gastroenterol Hepatol 18(3):151–166
3. Chen C et al (2023) Ganoderma lucidum polysaccharide inhibits HSC activation and liver fibrosis via targeting inflammation, apoptosis, cell cycle, and ECM-receptor interaction mediated by TGF-beta/Smad signaling. Phytomedicine 110:154626
4. Ma PF et al (2017) Cytotherapy with M1-polarized macrophages ameliorates liver fibrosis by modulating immune microenvironment in mice. J Hepatol 67(4):770–779
5. Yamamoto Y et al (2023) The heterogeneity of cancer-associated fibroblast subpopulations: their origins, biomarkers, and roles in the tumor microenvironment. Cancer Sci 114(1):16–24
6. Hammerich L, Tacke F (2023) Hepatic inflammatory responses in liver fibrosis. Nat Rev Gastroenterol Hepatol 20(10):633–646
7. Luo X et al (2018) Expression of STING Is Increased in Liver Tissues from patients with NAFLD and promotes macrophage-mediated hepatic inflammation and fibrosis in mice. Gastroenterology 155(6):1971-1984e4
8. Peiseler M et al (2023) Kupffer cell-like syncytia replenish resident macrophage function in the fibrotic liver. Science 381(6662):5202
9. Zhou Y et al (2022) CD4(+) T cell activation and inflammation in NASH-related fibrosis. Front Immunol 13:967410
10. Chen Y et al (2023) ALKBH5-mediated m(6) A demethylation of TIRAP mRNA promotes radiation-induced liver fibrosis and decreases radiosensitivity of hepatocellular carcinoma. Clin Transl Med 13(2):e1198
11. Brown ZJ et al (2023) Management of Hepatocellular carcinoma: a review. JAMA Surg 158(4):410–420
12. Song M et al (2021) Cancer-associated fibroblast-mediated cellular crosstalk supports hepatocellular carcinoma progression. Hepatology 73(5):1717–1735
13. Yu Z et al (2023) Tissue fibrosis induced by radiotherapy: current understanding of the molecular mechanisms, diagnosis and therapeutic advances. J Transl Med 21(1):708
14. Wojcieszynski AP, Ben-Josef E (2019) First do no harm; how to prevent liver decompensation after radiation therapy for hepatocellular carcinoma. Int J Radiat Oncol Biol Phys 105(1):87–89
15. Liu XQ et al (2020) Biomimetic matrix stiffness modulates hepatocellular carcinoma malignant phenotypes and macrophage polarization through multiple modes of mechanical feedbacks. ACS Biomater Sci Eng 6(7):3994–4004
16. Calitz C et al (2023) Influence of extracellular matrix composition on tumour cell behaviour in a biomimetic in vitro model for hepatocellular carcinoma. Sci Rep 13(1):748
17. Cheng Y et al (2025) Stromal architecture and fibroblast subpopulations with opposing effects on outcomes in hepatocellular carcinoma. Cell Discov 11(1):1
18. Fearon DT (2014) The carcinoma-associated fibroblast expressing fibroblast activation protein and escape from immune surveillance. Cancer Immunol Res 2(3):187–193
19. Li G et al (2015) Radiation-induced liver injury in three-dimensional conformal radiation therapy (3D-CRT) for postoperative or locoregional recurrent gastric cancer: risk factors and dose limitations. PLoS ONE 10(8):e0136288
20. McNamara ME et al (2023) Circulating cell-free methylated DNA reveals tissue-specific, cellular damage from radiation treatment. JCI insight 8(14):e156529
21. Llovet JM et al (2021) Hepatocellular carcinoma. Nat Rev Dis Primers 7(1):6
22. Xu L et al (2023) Doxofylline ameliorates liver fibrosis by regulating the ferroptosis signaling pathway. Front Pharmacol 14:1135366
23. Zhang Z et al (2023) ANGPTL8 accelerates liver fibrosis mediated by HFD-induced inflammatory activity via LILRB2/ERK signaling pathways. J Adv Res 47:41–56
24. Pinzani M (2023) When research on liver fibrosis made the right turn. Nat Rev Gastroenterol Hepatol 20(10):632
25. Wang Y et al (2024) Targeting Src SH3 domain-mediated glycolysis of HSC suppresses transcriptome, myofibroblastic

activation, and colorectal liver metastasis. Hepatology 80(3):578–594
26. Tsai YT et al (2022) Galectin-1 orchestrates an inflammatory tumor-stroma crosstalk in hepatoma by enhancing TNFR1 protein stability and signaling in carcinoma-associated fibroblasts. Oncogene 41(21):3011–3023
27. Zhang R et al (2020) STMN1 upregulation mediates hepatocellular carcinoma and hepatic stellate cell crosstalk to aggravate cancer by triggering the MET pathway. Cancer Sci 111(2):406–417
28. Xie M et al (2023) FGF19/FGFR4-mediated elevation of ETV4 facilitates hepatocellular carcinoma metastasis by upregulating PD-L1 and CCL2. J Hepatol 79(1):109–125
29. Zhou C et al (2023) Disruption of SLFN11 deficiency-induced CCL2 signaling and macrophage M2 polarization potentiates Anti-PD-1 therapy efficacy in hepatocellular carcinoma. Gastroenterol 164(7):1261–1278
30. Weng J et al (2024) Repolarization of immunosuppressive macrophages by targeting SLAMF7-regulated CCL2 signaling sensitizes hepatocellular carcinoma to immunotherapy. Cancer Res 84(11):1817–1833
31. Ezhilarasan D (2022) Hepatic stellate cells in the injured liver: Perspectives beyond hepatic fibrosis. J Cell Physiol 237(1):436–449
32. Geiss C et al (2022) Multistability in macrophage activation pathways and metabolic implications. Cells 11(3):404
33. Qian BZ, Pollard JW (2010) Macrophage diversity enhances tumor progression and metastasis. Cell 141(1):39–51
34. Xiong J et al (2024) Matrix stiffness affects tumor-associated macrophage functional polarization and its potential in tumor therapy. J Transl Med 22(1):85
35. Jiang Y et al (2022) Targeting extracellular matrix stiffness and mechanotransducers to improve cancer therapy. J Hematol Oncol 15(1):34
36. Poole K et al (2014) Tuning Piezo ion channels to detect molecular-scale movements relevant for fine touch. Nat Commun 5:3520
37. Solis AG et al (2019) Mechanosensation of cyclical force by PIEZO1 is essential for innate immunity. Nature 573(7772):69–74
38. Atcha H et al (2021) Mechanically activated ion channel Piezo1 modulates macrophage polarization and stiffness sensing. Nat Commun 12(1):3256
39. Leng S et al (2022) Ion channel Piezo1 activation promotes aerobic glycolysis in macrophages. Front Immunol 13:976482
40. Pyonteck SM et al (2013) CSF-1R inhibition alters macrophage polarization and blocks glioma progression. Nat Med 19(10):1264–1272
41. Tacke F, Zimmermann HW (2014) Macrophage heterogeneity in liver injury and fibrosis. J Hepatol 60(5):1090–1096
42. Klug F et al (2013) Low-dose irradiation programs macrophage differentiation to an iNOS(+)/M1 phenotype that orchestrates effective T cell immunotherapy. Cancer Cell 24(5):589–602
43. Wu Q et al (2017) Macrophage biology plays a central role during ionizing radiation-elicited tumor response. Biomed J 40(4):200–211
44. Shu Y, Cheng P (2020) Targeting tumor-associated macrophages for cancer immunotherapy. Biochim Biophys Acta Rev Cancer 1874(2):188434
45. Habanjar O et al (2022) Multistability in macrophage activation pathways and metabolic implications. Cells 11(3):404
46. Cheng X et al (2016) Antibody-mediated blockade of phosphatidylserine enhances the antitumor effect of sorafenib in hepatocellular carcinomas xenografts. Ann Surg Oncol 23(Suppl 5):583–591
47. Chen R et al (2022) Modulation of the tumour microenvironment in hepatocellular carcinoma by tyrosine kinase inhibitors: from modulation to combination therapy targeting the microenvironment. Cancer Cell Int 22(1):73
48. Liu Y et al (2023) Identification of a tumour immune barrier in the HCC microenvironment that determines the efficacy of immunotherapy. J Hepatol 78(4):770–782
49. Han S et al (2023) d-lactate modulates M2 tumor-associated macrophages and remodels immunosuppressive tumor microenvironment for hepatocellular carcinoma. Sci Adv 9(29):eadg2697
50. Jiang Y et al (2021) Promotion of epithelial-mesenchymal transformation by hepatocellular carcinoma-educated macrophages through Wnt2b/beta-catenin/c-Myc signaling and reprogramming glycolysis. J Exp Clin Cancer Res 40(1):13
51. Chen L et al (2023) Radiation therapy in the era of immune treatment for hepatocellular carcinoma. Front Immunol 14:1100079
52. Sung W et al (2022) Mathematical modeling to simulate the effect of adding radiation therapy to immunotherapy and application to hepatocellular carcinoma. Int J Radiat Oncol Biol Phys 112(4):1055–1062
53. Jiang J et al (2022) Stereotactic body radiation therapy (SBRT) plus immune checkpoint inhibitors (ICI) in hepatocellular carcinoma and cholangiocarcinoma. Cancers 15(1):50
54. Hiam-Galvez KJ, Allen BM, Spitzer MH (2021) Systemic immunity in cancer. Nat Rev Cancer 21(6):345–359
55. Peng H, Zhu E, Zhang Y (2022) Advances of cancer-associated fibroblasts in liver cancer. Biomark Res 10(1):59
56. Kalluri R (2016) The biology and function of fibroblasts in cancer. Nat Rev Cancer 16(9):582–598
57. Fiori ME et al (2019) Cancer-associated fibroblasts as abettors of tumor progression at the crossroads of EMT and therapy resistance. Mol Cancer 18(1):70
58. Prakash J (2016) Cancer-associated fibroblasts: perspectives in cancer therapy. Trends Cancer 2(6):277–279
59. Akkiz H (2023) Emerging Role of Cancer-Associated Fibroblasts in Progression and Treatment of Hepatocellular Carcinoma. Int J Mol Sci 24(4):3941
60. Biffi G, Tuveson DA (2021) Diversity and biology of cancer-associated fibroblasts. Physiol Rev 101(1):147–176
61. Ohlund D et al (2017) Distinct populations of inflammatory fibroblasts and myofibroblasts in pancreatic cancer. J Exp Med 214(3):579–596
62. Elyada E et al (2019) Cross-species single-cell analysis of pancreatic ductal adenocarcinoma reveals antigen-presenting cancer-associated fibroblasts. Cancer Discov 9(8):1102–1123
63. Zhang J, Tian XJ, Xing J (2016) Signal transduction pathways of EMT induced by TGF-beta, SHH, and WNT and their crosstalks. J Clin Med 5:4
64. Wehrli M et al (2024) Mesothelin CAR T cells secreting anti-FAP/anti-CD3 molecules efficiently target pancreatic adenocarcinoma and its stroma. Clin Cancer Res 30(9):1859–1877
65. Feig C et al (2013) Targeting CXCL12 from FAP-expressing carcinoma-associated fibroblasts synergizes with anti-PD-L1 immunotherapy in pancreatic cancer. Proc Natl Acad Sci U S A 110(50):20212–20217
66. Grout JA et al (2022) Spatial positioning and matrix programs of cancer-associated fibroblasts promote T-cell exclusion in human lung tumors. Cancer Discov 12(11):2606–2625
67. Stanisavljevic J et al (2015) Snail1-expressing fibroblasts in the tumor microenvironment display mechanical properties that support metastasis. Cancer Res 75(2):284–295
68. Ferrari N et al (2019) Dickkopf-3 links HSF1 and YAP/TAZ signalling to control aggressive behaviours in cancer-associated fibroblasts. Nat Commun 10(1):130
69. Calvo F et al (2013) Mechanotransduction and YAP-dependent matrix remodelling is required for the generation and maintenance of cancer-associated fibroblasts. Nat Cell Biol 15(6):637–646

70. Zhou H et al (2014) Fasudil hydrochloride hydrate, a Rho-kinase inhibitor, ameliorates hepatic fibrosis in rats with type 2 diabetes. Chin Med J (Engl) 127(2):225–231
71. Licaj M et al (2024) Residual ANTXR1+ myofibroblasts after chemotherapy inhibit anti-tumor immunity via YAP1 signaling pathway. Nat Commun 15(1):1312
72. Tian B et al (2017) Urokinase plasminogen activator secreted by cancer-associated fibroblasts induces tumor progression via PI3K/AKT and ERK signaling in esophageal squamous cell carcinoma. Oncotarget 8(26):42300–42313
73. Wang J et al (2021) PDGF-BB induces conversion, proliferation, migration, and collagen synthesis of oral mucosal fibroblasts through PDGFR-beta/PI3K/ AKT signaling pathway. Cancer Biomark 30(4):407–415
74. Yoon H et al (2021) Cancer-associated fibroblast secretion of PDGFC promotes gastrointestinal stromal tumor growth and metastasis. Oncogene 40(11):1957–1973
75. Borriello L et al (2017) Cancer-associated fibroblasts share characteristics and protumorigenic activity with mesenchymal stromal cells. Cancer Res 77(18):5142–5157
76. Fu C et al (2019) FSP1 promotes the biofunctions of adventitial fibroblast through the crosstalk among RAGE, JAK2/STAT3 and Wnt3a/beta-catenin signalling pathways. J Cell Mol Med 23(11):7246–7260
77. Song D et al (2024) Insulin-like growth factor 2 drives fibroblast-mediated tumor immunoevasion and confers resistance to immunotherapy. J Clin Invest 134:22
78. Li H et al (2025) Disrupting AGR2/IGF1 paracrine and reciprocal signaling for pancreatic cancer therapy. Cell Rep Med 6(2):101927
79. Du L et al (2019) IGF-2 preprograms maturing macrophages to acquire oxidative phosphorylation-dependent anti-inflammatory properties. Cell Metab 29(6):1363-1375 e8
80. Mizutani Y et al (2019) Meflin-positive cancer-associated fibroblasts inhibit pancreatic carcinogenesis. Cancer Res 79(20):5367–5381
81. Ando R et al (2024) Meflin is a marker of pancreatic stellate cells involved in fibrosis and epithelial regeneration in the pancreas. J Pathol 262(1):61–75
82. Feng Y et al (2024) M2-Type macrophages and cancer-associated fibroblasts combine to promote colorectal cancer liver metastases. Onco Targets Ther 17:243–260
83. Chen X, Song E (2019) Turning foes to friends: targeting cancer-associated fibroblasts. Nat Rev Drug Discov 18(2):99–115
84. Geyer N, Gerling M (2021) Hedgehog signaling in colorectal cancer: all in the stroma? Int J Mol Sci 22(3):1025
85. Miyai Y et al (2020) Cancer-associated fibroblasts that restrain cancer progression: hypotheses and perspectives. Cancer Sci 111(4):1047–1057
86. Shin K et al (2014) Hedgehog signaling restrains bladder cancer progression by eliciting stromal production of urothelial differentiation factors. Cancer Cell 26(4):521–533
87. Chen Y, McAndrews KM, Kalluri R (2021) Clinical and therapeutic relevance of cancer-associated fibroblasts. Nat Rev Clin Oncol 18(12):792–804
88. Wu SZ et al (2020) Stromal cell diversity associated with immune evasion in human triple-negative breast cancer. EMBO J 39(19):e104063
89. Ozdemir BC et al (2014) Depletion of carcinoma-associated fibroblasts and fibrosis induces immunosuppression and accelerates pancreas cancer with reduced survival. Cancer Cell 25(6):719–734
90. Dziadek S et al (2024) Comprehensive analysis of fibroblast activation protein expression across 23 tumor indications: insights for biomarker development in cancer immunotherapies. Front Immunol 15:1352615
91. Yu G et al (2013) Hepatic stellate cells secreted hepatocyte growth factor contributes to the chemoresistance of hepatocellular carcinoma. PLoS ONE 8(9):e73312
92. Christiansen VJ et al (2007) Effect of fibroblast activation protein and alpha2-antiplasmin cleaving enzyme on collagen types I, III, and IV. Arch Biochem Biophys 457(2):177–186
93. Morikawa S et al (2002) Abnormalities in pericytes on blood vessels and endothelial sprouts in tumors. Am J Pathol 160(3):985–1000
94. Santos AM et al (2009) Targeting fibroblast activation protein inhibits tumor stromagenesis and growth in mice. J Clin Invest 119(12):3613–3625
95. Kelly T et al (1998) Seprase, a membrane-bound protease, is overexpressed by invasive ductal carcinoma cells of human breast cancers. Mod Pathol 11(9):855–863
96. Iwasa S et al (2005) Increased expression of seprase, a membrane-type serine protease, is associated with lymph node metastasis in human colorectal cancer. Cancer Lett 227(2):229–236
97. Augoff K et al (2014) Upregulated expression and activation of membrane-associated proteases in esophageal squamous cell carcinoma. Oncol Rep 31(6):2820–2826
98. Ammirante M et al (2014) Tissue injury and hypoxia promote malignant progression of prostate cancer by inducing CXCL13 expression in tumor myofibroblasts. Proc Natl Acad Sci U S A 111(41):14776–14781
99. Levy MT et al (2002) Intrahepatic expression of the hepatic stellate cell marker fibroblast activation protein correlates with the degree of fibrosis in hepatitis C virus infection. Liver 22(2):93–101
100. Lee J et al (2022) Fibroblast activation protein activated antifibrotic peptide delivery attenuates fibrosis in mouse models of liver fibrosis. Nat Commun 13(1):1516
101. Zou B et al (2018) The expression of FAP in hepatocellular Carcinoma cells is induced by hypoxia and correlates with poor clinical outcomes. J Cancer 9(18):3278–3286
102. Yang AT et al (2023) Fibroblast activation protein activates macrophages and promotes parenchymal liver inflammation and fibrosis. Cell Mol Gastroenterol Hepatol 15(4):841–867
103. Avery D et al (2018) Extracellular matrix directs phenotypic heterogeneity of activated fibroblasts. Matrix Biol 67:90–106
104. Affo S et al (2021) Promotion of cholangiocarcinoma growth by diverse cancer-associated fibroblast subpopulations. Cancer Cell 39(6):866-882e11
105. Cai J et al (2023) A multifactorial analysis of FAP to regulate gastrointestinal cancers progression. Front Immunol 14:1183440
106. Peng H et al (2020) Cancer-associated fibroblasts enhance the chemoresistance of CD73(+) hepatocellular carcinoma cancer cells via HGF-Met-ERK1/2 pathway. Ann Transl Med 8(14):856
107. Levy MT et al (1999) Fibroblast activation protein: a cell surface dipeptidyl peptidase and gelatinase expressed by stellate cells at the tissue remodelling interface in human cirrhosis. Hepatology 29(6):1768–1778
108. Kim J, Seki E (2023) FAP: not just a biomarker but druggable target in liver fibrosis. Cell Mol Gastroenterol Hepatol 15(4):1018–1019
109. Wang XM et al (2005) Fibroblast activation protein increases apoptosis, cell adhesion, and migration by the LX-2 human stellate cell line. Hepatology 42(4):935–945
110. Gao Y et al (2022) Radiation-induced FAP + fibroblasts are involved in keloid recurrence after radiotherapy. Front Cell Dev Biol 10:957363
111. Fischer LS et al (2021) Molecular force measurement with tension sensors. Annu Rev Biophys 50:595–616
112. Wong VW et al (2011) Mechanical force prolongs acute inflammation via T-cell-dependent pathways during scar formation. FASEB J 25(12):4498–4510

113. Liu H et al (2022) Piezo1 channels as force sensors in mechanical force-related chronic inflammation. Front Immunol 13:816149
114. Joshi H, Morley SC (2019) Cells under stress: the mechanical environment shapes inflammasome responses to danger signals. J Leukoc Biol 106(1):119–125
115. Orsini EM et al (2021) Stretching the function of innate immune cells. Front Immunol 12:767319
116. Saraswathibhatla A, Indana D, Chaudhuri O (2023) Cell-extracellular matrix mechanotransduction in 3D. Nat Rev Mol Cell Biol 24(7):495–516
117. Geng J et al (2021) TLR4 signalling via Piezo1 engages and enhances the macrophage mediated host response during bacterial infection. Nat Commun 12(1):3519
118. Taufalele PV et al (2023) Matrix stiffness enhances cancer-macrophage interactions and M2-like macrophage accumulation in the breast tumor microenvironment. Acta Biomater 163:365–377
119. Lu Y et al (2023) Calponin 1 increases cancer-associated fibroblasts-mediated matrix stiffness to promote chemoresistance in gastric cancer. Matrix Biol 115:1–15
120. Herrera M et al (2013) Cancer-associated fibroblast and M2 macrophage markers together predict outcome in colorectal cancer patients. Cancer Sci 104(4):437–444
121. Nagarsheth N, Wicha MS, Zou W (2017) Chemokines in the cancer microenvironment and their relevance in cancer immunotherapy. Nat Rev Immunol 17(9):559–572
122. Li YM et al (2022) Piezo1 promoted hepatocellular carcinoma progression and EMT through activating TGF-beta signaling by recruiting Rab5c. Cancer Cell Int 22(1):162
123. Liang D et al (2023) Targeting extracellular matrix through phytochemicals: a promising approach of multi-step actions on the treatment and prevention of cancer. Front Pharmacol 14:1186712
124. Zhang X et al (2022) Piezo1-mediated mechanosensation in bone marrow macrophages promotes vascular niche regeneration after irradiation injury. Theranostics 12(4):1621–1638
125. Huang JQ et al (2021) Mechanically activated calcium channel PIEZO1 modulates radiation-induced epithelial-mesenchymal transition by forming a positive feedback with TGF-beta1. Front Mol Biosci 8:725275
126. Luo S et al (2023) Piezo1 specific deletion in macrophage protects the progression of liver fibrosis in mice. Theranostics 13(15):5418–5434
127. Straub JM et al (2015) Radiation-induced fibrosis: mechanisms and implications for therapy. J Cancer Res Clin Oncol 141(11):1985–1994
128. Klingberg F, Hinz B, White ES (2013) The myofibroblast matrix: implications for tissue repair and fibrosis. J Pathol 229(2):298–309
129. Shu G et al (2021) Piperine inhibits AML-12 hepatocyte EMT and LX-2 HSC activation and alleviates mouse liver fibrosis provoked by CCl(4): roles in the activation of the Nrf2 cascade and subsequent suppression of the TGF-beta1/Smad axis. Food Funct 12(22):11686–11703
130. Shu G et al (2022) Limonin relieves TGF-beta-induced hepatocyte EMT and hepatic stellate cell activation in vitro and CCl(4)-induced liver fibrosis in mice via upregulating Smad7 and subsequent suppression of TGF-beta/Smad cascade. J Nutr Biochem 107:109039
131. Dai C et al (2021) A characterized saponin extract of Panax japonicus suppresses hepatocyte EMT and HSC activation in vitro and CCl(4)-provoked liver fibrosis in mice: Roles of its modulatory effects on the Akt/GSK3beta/Nrf2 cascade. Phytomedicine 93:153746
132. Bai Y et al (2019) Mesenchymal stem cells reverse diabetic nephropathy disease via Lipoxin A4 by targeting transforming growth factor beta (TGF-beta)/smad pathway and pro-inflammatory cytokines. Med Sci Monit 25:3069–3076
133. Kim H et al (2020) LXA(4)-FPR2 signaling regulates radiation-induced pulmonary fibrosis via crosstalk with TGF-beta/Smad signaling. Cell Death Dis 11(8):653
134. Azimi I (2018) The interplay between HIF-1 and calcium signalling in cancer. Int J Biochem Cell Biol 97:73–77
135. Nie X et al (2022) Kinsenoside protects against radiation-induced liver fibrosis via downregulating connective tissue growth factor through TGF-beta1 signaling. Front Pharmacol 13:808576
136. Zuo T et al (2023) Macrophage-derived Cathepsin S Remodels the extracellular matrix to promote liver fibrogenesis. Gastroenterology 165(3):746–761