Unraveling the roles of fibroblast activation protein-positive cancer-associated fibroblasts in cancer: From mechanisms to therapy (Review)

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Received February 11, 2026; Accepted June 2, 2026

DOI: 10.3892/ijo.2026.5903

Abstract. Cancer-associated fibroblasts (CAFs) in the tumor microenvironment (TME) are involved in tumor pathogenesis. Fibroblast activation protein (FAP)$^+$ CAFs are the predominant CAF subtype across multiple cancer types, including breast, lung and pancreatic cancer. FAP$^+$ CAFs are crucial contributors to tumor progression. However, incomplete understanding of the biology of FAP$^+$ CAFs limits their potential for clinical application. The present review aimed to summarize the characteristic features, functions and underlying mechanisms of FAP$^+$ CAFs in tumor growth, including their involvement in extracellular matrix organization, tumor expansion and immunomodulation within the TME, in which FAP plays an important role, and FAP$^+$ CAF-based strategies for tumor diagnosis and therapeutic intervention. The present study aimed to provide a conceptual framework for the multifaceted roles of FAP$^+$ CAFs in cancer progression to guide development of optimized FAP$^+$ CAF-targeted diagnostics and therapies.

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Abbreviations: FAP, fibroblast activation protein; ECM, extracellular matrix; TME, tumor microenvironment; ap, antigen-presenting; iCAF, inflammatory cancer-associated fibroblast; my, myofibroblastic

Key words: cancer-associated fibroblast, fibroblast activation protein, tumor progression, tumor microenvironment, cancer therapy

1. Introduction

Since the 'seed and soil' theory was proposed in 1889 to describe the association between tumor cells and their surrounding environment (1), a growing number of researchers have recognized the importance of the tumor microenvironment (TME) in tumor development (2-4). As the 'soil' for tumor cell growth, the TME contains nutrients, regulatory factors, extracellular matrix (ECM), intertwined blood vessels and diverse stromal and immune cells (5). Interactions between the components within the TME drive dynamic changes and the alterations of properties or quantities in certain components, such as decreased T cell function, increased stromal density and rising levels of inflammatory cytokines, may affect tumor growth (3). Cancer-associated fibroblasts (CAFs) are prominent stromal cells within the TME and influence tumor behavior through multiple complex mechanisms (4). Furthermore, they impede the efficacy of various tumor therapies, including radiotherapy, chemotherapy and immunotherapy by enhancing tumor cell stemness and eliciting immunosuppression (5,6).

CAF characterization primarily relies on morphology (elongated or stellate shape), biological properties and expression of canonical biomarkers including α smooth muscle actin (α-SMA), vimentin, fibroblast activation protein (FAP), platelet-derived growth factor receptors (PDGFRs), podoplanin, periostin (POSTN), transgelin (TAGLN), collagen (COL)1A1, COL1A2 and S100A4 (7). However, that these markers are not universally co-expressed across all CAFs (6). For example, in glioblastoma, the majority of CAFs co-expressing FAP and PDGFRβ are negative for α-SMA (6). Multiplex immunohistochemical analysis in pancreatic cancer has revealed that only a minor subset of CAFs co-express α-SMA and FAP (8). Markers such as COL1A1, COL1A2, PDGFRα and vimentin are broadly distributed across diverse CAF populations, whereas others, including TAGLN, FAP, S100A4, α-SMA and

PDGFRβ, display notable subpopulation-restricted enrichment (9). This phenomenon has been conceptualized as CAF heterogeneity, spurring the development of CAF classification frameworks grounded in transcriptional profiles or functional characteristics (9).

Among CAF-related markers, FAP shows the strongest association with other markers (10). It is a type II transmembrane glycoprotein possessing dual dipeptidyl peptidase and gelatinase/collagenase activity (10). Notably, evidence has revealed the protease-independent roles of FAP as a signaling molecule participating in the regulation of multiple signaling pathways (10). FAP+ CAFs are a CAF subset characterized by high FAP expression. The abundance of FAP+ CAFs increases with advancing tumor stage (11). Given their prominent pro-tumor functions, FAP+ CAFs have garnered notable attention in the field of tumor stroma research in recent years (12,13). The cell surface localization of FAP also allows efficient isolation of FAP+ CAFs via fluorescence-activated cell sorting, facilitating experimental characterization and mechanistic investigation (6).

The present review aimed to summarize the cellular origins, spatial distribution and function of FAP+ CAFs from a dual perspective as a practical marker delineating the FAP+ CAF subset and a functional molecule actively shaping a distinct TME. In addition, the present study aimed to evaluate diagnostic and therapeutic strategies targeting FAP+ CAFs and summarize their potential for combination with existing clinical regimens. The present review aimed to provide an overall framework outlining the roles of FAP+ CAFs in tumor progression, diagnosis and treatment to promote their translational application.

2. FAP+ CAFs

CAFs represent a highly heterogeneous cell population. They originate from diverse precursors including resident fibroblasts, bone marrow-derived mesenchymal stem cells, epithelial cells and endothelial cells, macrophages, pericytes and adipocytes, each of which is driven by distinct activation signals to acquire a unique CAF-like phenotype (14). There are concomitantly harbored anti- and pro-tumorigenic and functionally neutral CAFs in tumor stroma (7,9). Different CAF subtypes exhibit distinct gene expression profiles, serve dynamic roles in tumor progression and show differential associations with therapy responses and clinical outcomes (8). FAP+ CAFs represent one of the most prevalent CAF populations, therefore, understanding of their distribution, unique features and the mechanisms driving their expansion is fundamental for decoding how stromal cells behave and function in malignant progression and identifying stage-specific therapeutic vulnerabilities.

Spatial landscape of FAP and FAP+ CAFs. FAP serves not only as a key marker for identifying FAP+ CAFs but also as a functional protein with biological roles (15). *In vivo,* FAP exists primarily in two isoforms: A membrane-bound and a soluble form (16). Soluble FAP (sFAP) is detectable in both the TME and the plasma of patients with cancer (16,17). In colorectal cancer, plasma sFAP levels are inversely associated with tumor size, depth of invasion and overall survival (17). However, circulating sFAP is not derived from tumor tissue but from physiological sources such as skeletal muscle, liver and bone marrow, and may reflect a systemic host response to malignancy, analogous to the decline in plasma levels of negative acute-phase proteins during acute inflammation (17). The membrane-bound form is expressed on the cell surface. Although FAP expression in cancer has been documented in other cell types, including tumor, endothelial and immune cells and pericytes (18,19), its most prominent expression is consistently observed in CAFs (18,20).

From a tissue localization perspective, FAP is highly expressed in inflammatory lesions and tumor tissue, which are marked by common pathological features such as tissue remodeling, angiogenesis and immune cell infiltration (21). By contrast, FAP expression is low in most normal and adjacent non-neoplastic tissue (22). Analysis of transcriptomic data from the Human Protein Atlas database reveals that elevated FAP expression is commonly observed in tumor tissue from patients with various solid malignancies, including colorectal, gastric, breast, pancreatic and prostate cancer (23) (Fig. 1). These data suggest that FAP may serve as a potential biomarker associated with malignant progression.

Similar to the distribution pattern of FAP in tumors, immunohistochemical staining and spatial transcriptomic analyses have revealed that FAP+ CAFs are widely distributed across multiple tumor types, such as breast, lung and pancreatic cancer, while exhibiting a degree of tissue-specific spatial preference (9,13,21). In colorectal cancer and hepatocellular carcinoma, FAP+ CAFs are typically enriched at the invasive tumor margin, a position that facilitates their interaction with tumor-infiltrating immune cells such as macrophages and T cells (24,25). Additionally, FAP+ CAFs accumulate in perivascular niches or localize near both cancer and immune cells (26). Collectively, FAP and FAP+ CAFs exhibit concordant spatial distribution patterns, with both concentrating in functional niches associated with metastasis, angiogenesis and immune cell infiltration (18,21). Thus, the detection of FAP expression has been widely adopted as a practical method for inferring the abundance and distribution of FAP+ CAFs in malignant tumors (21,27,28).

Differences between FAP+ CAFs and other CAF subtypes. Based on the expression of classic CAF markers, CAF have been primarily stratified into FAP+ and α-SMA+ subsets in multiple studies (9,29,30). There is a less prevalent but consistently observed CAF population co-expressing elevated levels of both FAP and α-SMA (FAP+ α-SMA+ CAFs) (31,32). By contrast, certain current studies have categorized CAFs into three major functional subpopulations: Myofibroblastic CAFs (myCAFs), inflammatory CAFs (iCAFs) and antigen-presenting CAFs (apCAFs) based on gene expression profiles, spatial distribution and functional markers (33,34). Of note, the CAF subsets defined by these classification systems share similarities in their molecular signatures and dominant signaling pathways (Fig. 2).

α-SMA+ CAFs (characterized by high α-SMA and low FAP expression) align with the myCAF phenotype and function (32,33,35,36), while FAP+ CAFs (typically high in FAP but low in α-SMA) exhibit phenotypical and functional features that largely overlap with those of iCAFs (37). apCAFs are

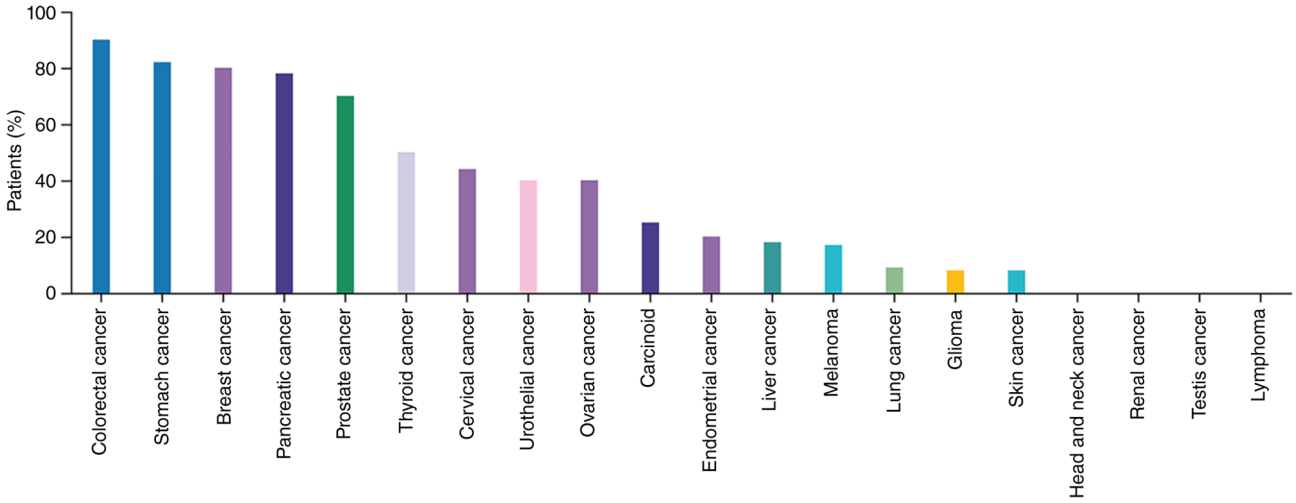

Figure 1. Expression profile of FAP across human cancer. The bar indicates the percentage of patients (n=4-12) with high or medium FAP protein expression based on antibody staining. Data were obtained from the Human Protein Atlas (proteinatlas.org). FAP, fibroblast activation protein.

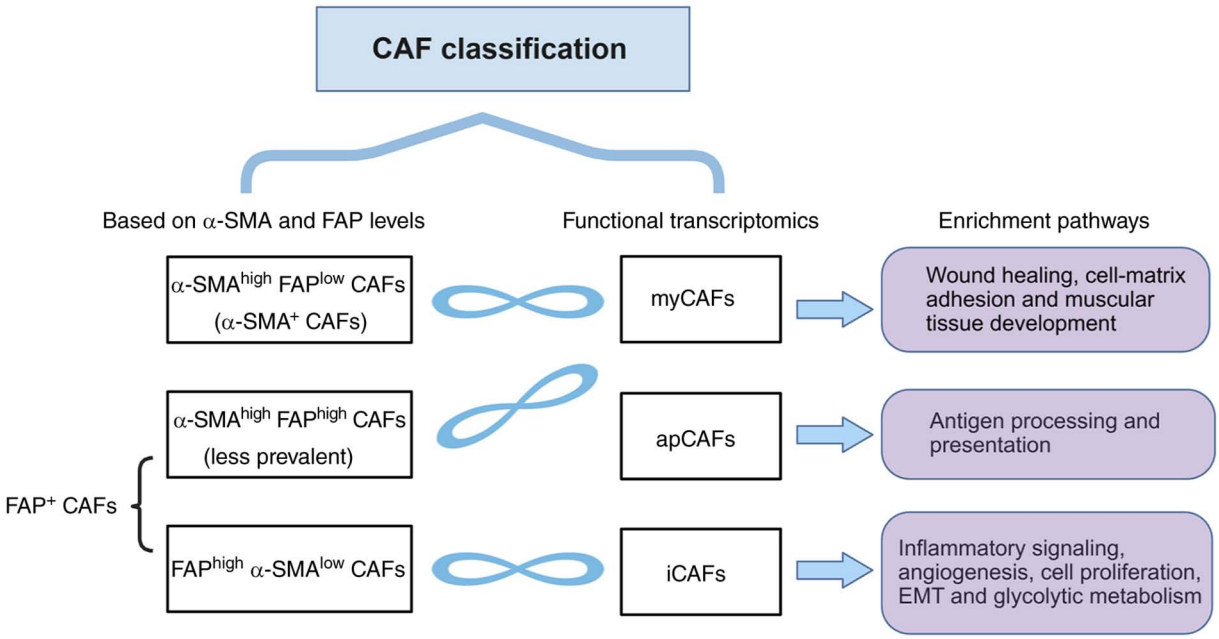

Figure 2. Marker- and function-defined CAF subsets. α-SMA$^+$ CAFs (α-SMA^{high} FAP^{low} CAFs) largely correspond to myCAFs. The majority of FAP$^+$ CAFs exhibit iCAF-like functional states, whereas a minor proportion of double-positive subset (α-SMA^{high} FAP^{high} CAFs) display a myCAF-like phenotype. SMA, smooth muscle actin; myCAF, myofibroblastic cancer-associated fibroblast; FAP, fibroblast activation protein; i, inflammatory; ap, antigen-presenting.

active in antigen presentation and serve a dual role in tumor immunity by engaging in both immune activation and suppression (37,38). The spatial distribution of these CAF subtypes also shows distinct features. Unlike FAP$^+$ CAFs, α-SMA$^+$ CAFs are predominantly localized within the peritumoral stromal region (31). apCAFs exhibit a unique compartmentalized distribution pattern, with a tendency to form organized cell clusters adjacent to tertiary lymphoid structures (37). From a cell behavior perspective, FAP expression confers distinct capabilities. FAP$^+$ CAFs exhibit markedly higher COL contractility than FAP$^-$ CAFs and increasing FAP expression in CAFs further enhances this COL contractile capacity (39). In addition, FAP$^+$ CAFs demonstrate superior survival adaptability relative to their FAP-negative counterparts. Experimental data show that under standard *in vitro* culture conditions with 10% FBS, FAP$^+$ CAFs have markedly higher proliferative activity than CAFs with low FAP expression (40).

Recent studies have defined additional novel CAF population subgroups based on unique gene expression profiles or functions, including zinc-transporter$^+$, S100A4$^+$, POSTN$^+$ and CD36$^+$ CAFs (41,42). Table I outlines notable CAF subtypes and their key features and functions associated with tumor growth. Unlike FAP$^+$ CAFs, most newly identified CAF subsets lack highly specific surface markers, which limits their isolation, functional characterization and therapeutic targeting (43). FAP defines a CAF cluster that encompasses both myCAF- and iCAF-like states yet shares a common molecular tag. Certain newly identified subsets such as mCAFs, PDPN$^+$ CAFs

Table I. Functional and mechanistic comparison of FAP+ CAFs with other CAF subsets.

CAF subset	Cancer type	Role	Functional mechanisms	(Refs.)
α-SMA^{high} FAP^{low}	PC, BC, OV, LC, OSCC	Controversial	Suppress tumor growth by regulating T cells, partly via type I collagen; promote tumor growth via OPN; promote cancer metastasis via type III collagen; promote tumor invasion via OXTR/ERK5	(8,9,29,35, 36,123)
α-SMA^{high} FAP^{high}	BC	Tumor-promoting	Unknown	(8,9,31,32)
α-SMA^{low} FAP^{high}	GC, OC, BC, LC, OSCC, PDAC	Tumor-promoting	Promote tumor growth, invasion and metastasis; suppress immune response	(9,21,30,39, 124,125)
apCAFs (S100A4+)	GC, BC, LC, PDAC	Controversial	Strengthen antitumor immunity by activating T cells; induce naive CD4+ T cell differentiation into Tregs	(33,37, 38,126)
POSTN+	BC, HCC	Tumor-promoting	Induce immunosuppression by blocking T cell infiltration and engaging SPP1+ macrophages	(44,127)
CD36+	HCC	Tumor-promoting	Inhibit antitumor immunity via MIF upregulation and MDSC recruitment	(52)
ZIP1+	LC	Tumor-promoting	Confer chemoresistance by transferring Zn^{2+} to cancer cells	(128)
Periostin+	CCA	Tumor-promoting	Promote tumor metastasis by activating integrin/FAK/Src-VE-cadherin signaling	(129)

apCAF, antigen-presenting cancer-associated fibroblast; FAP, fibroblast activation protein; PC, pancreatic cancer; BC, breast cancer; OV, ovarian cancer; LC, lung cancer; OSCC, oral squamous cell carcinoma; GC, gastric cancer; PDAC, pancreatic ductal adenocarcinoma; OPN, osteopontin; OXTR, oxytocin receptor; MIF, macrophage migration inhibitory factor; Treg, regulatory T cell; MDSC, myeloid-derived suppressor cell; SMA, smooth muscle actin; SPP, secreted phosphoprotein; VE, vascular endothelial.

and POSTN+ CAFs may represent further subdivisions within this framework based on differences in functional preference (31,43,44). Therefore, evaluating FAP expression status is key for future characterization of novel CAF subsets, which may not only provide an established molecular tag but also enrich the FAP+ CAF functional map while avoiding confusion arising from an overly detailed classification system.

Enhanced proportion of FAP+ CAFs in cancer. The proportion of FAP+ CAFs undergoes dynamic shifts that are associated with clinical tumor stage (44,45). For example, in breast cancer, FAP+ CAF populations show progressive expansion during tumor progression and become the predominant CAF subset in advanced stages (46). *In vitro* studies have identified that several cell sources, including pericytes (12), macrophages (47), normal fibroblasts (48), mesothelial cells (49) and mesenchymal stem cells (MSCs) (50), transdifferentiate to FAP+ CAFs. Among these, normal fibroblasts located in the peritumoral stroma may be the primary origin. In breast cancer, CD26+ normal fibroblasts transform into FAP+ CAFs, whereas CD26- normal fibroblasts differentiate into myCAFs (51). However, the primary source of FAP+ CAFs in other tumor types remains unclear. This ontological diversity of FAP+ CAFs within distinct tumor contexts may contribute to the dynamic changes in their abundance, as well as the variation in their phenotypic and functional states.

In addition to their direct origin, FAP+ CAFs arise from the trans-differentiation of other CAF subtypes. For example, CXCL14+ CAFs have been confirmed to differentiate into FAP+ CAFs (11). In renal cell carcinoma, cysteinyl leukotriene receptor 2 (CYSLTR2)+ CAFs represent a transitional cell state during phenotypic conversion toward the FAP+ CAF lineage (12). CytoTRACE analysis, a computational framework for predicting differentiation states from scRNA-seq data, indicates that among the notable CAF subtypes, FAP+ CAFs exhibit the lowest differentiation potential (11). These findings suggest FAP+ CAFs may represent a terminal state within the CAF lineage, implying a unidirectional phenotypic convergence where other CAF subtypes are more likely to convert into FAP+ CAFs than the reverse (12).

Evidence links the generation of FAP+ CAFs with elevated levels of cytokines, including TGF-β, TNF-α, IFN-γ, IL-17, IL-13, IL-12, IL-10, IL-6, IL-2 and IL-1 (21,52). Concurrently, environmental stressors and chemical cues constitute a critical regulatory layer that governs the phenotypic transition to a FAP+ CAF state (53,54). For example, hypoxia can induce fibroblasts to acquire inflammatory gene expression signatures and work with tumor cell-derived cytokines to promote an FAP+ CAF phenotype through hypoxia-inducible factor 1α-dependent mechanisms (53). Lactate, a key metabolic mediator that accumulates abundantly within the TME, promotes the functional transformation of MSCs into FAP+ CAFs, thereby driving

Table II. Key factors driving FAP+ CAFs differentiation from cells of origin.

Factor	Origin cell	Biological effect	(Refs.)
TGF-β	Normal fibroblasts	Upregulating FAP in a time- and dose-dependent manner	(78,130,131)
TNF-α, IL-1β	Mesenchymal stem cells	Upregulating FAP in a time- and dose-dependent manner	(132,133)
CCL18	Normal fibroblasts	Unknown	(134)
IL-17a	Hepatic stellate cells	Activating the STAT3 signaling pathway	(135)
Biglycan	Mesothelial cells	Activating the NF-κB pathway by binding to TLR2/TLR4	(49)
circNOX4	Normal fibroblasts	Sponging miR-329-5p that binds the 3'-UTR of FAP	(48)
Hypoxia	Normal fibroblasts	Upregulating FAP in a HIF1α-dependent manner	(53)
Lactate	Mesenchymal stem cells	Inducing H4K8 lactylation to promote FAP transcription	(54)

FAP, fibroblast activation protein; TGF-β, transforming growth factor-β; TNF-α, tumor necrosis factor-α; CCL, C-C motif ligand; TLR, toll-like receptor; HIF-1α, hypoxia-inducible factor-1α; circNOX4, circular RNA NADPH oxidase 4; miR, microRNA; UTR, untranslated region.

tumor growth (54). Regulatory factors and cell origins of FAP+ CAFs are summarized in Table II.

To date, endogenous or pharmacological factors capable of inhibiting the generation of FAP+ CAFs remain poorly characterized. Oxytocin suppresses colorectal cancer progression, in part through the downregulation of FAP expression (55). Autophagy may be key for maintaining the FAP+ CAF phenotype within the TME (56). A deeper understanding of the mechanisms regulating the generation of FAP+ CAFs may provide avenues to remodel the stromal microenvironment by inhibiting the conversion of CAFs into a tumor-promoting state, thereby informing the development of novel therapeutic strategies.

3. FAP+ CAF function in cancer progression

The cell properties and spatial distribution of FAP+ CAFs enable them to mediate communication with both the surrounding stromal environment and adjacent cells, shaping tumor pathogenesis across multiple aspects. Mechanistically, the protumor effects of FAP+ CAFs are primarily attributed to three interconnected axes: Remodeling of the ECM; enhancement of malignant phenotypes in tumor cells, including proliferation, invasion and drug resistance; and induction of an immunosuppressive microenvironment (Fig. 3) (57).

Roles of FAP+ CAFs in ECM remodeling and angiogenesis. Integrated transcriptomic, proteomic and functional studies have demonstrated the pro-fibrotic capacity of FAP+ CAFs, enabling efficient synthesis of key ECM components such as COL and fibronectin (27,39). FAP+ CAFs highly express the COL11A1 gene, as well as COL1A1 and COL1A2 (encoding type I COL), all of which are key components of the ECM scaffold (58). Spatial analysis in glioblastoma has confirmed that COL and fibronectin concentrations in FAP-high regions exceed those in FAP-low areas by more than threefold (59). Notably, treatment with specific FAP inhibitors (FAPIs) decreases the abnormal COL deposition (60), providing evidence for the central role of FAP+ CAFs in ECM synthesis.

In addition to contributing to ECM synthesis, FAP+ CAFs actively contract the ECM, creating a dense, rigid TME that blocks immune cell infiltration and promotes immune evasion (39,61). However, tumor cells are not constrained by this barrier as they can remodel the surrounding matrix and create paths for invasion within the dense ECM through upregulated matrix metalloproteinases and activated integrin signaling pathways (62). FAP+ CAFs alter ECM ultrastructure, enabling functional tissue reorganization that favors tumor cell metastasis. For example, *in vitro* 3D culture models have revealed that FAP+ CAFs align ECM fibers into parallel, linear topographical cues, which markedly promotes both the efficiency and directional persistence of cancer cell invasion (63,64). This organized alignment is not observed in the matrix adjacent to other CAF subsets (64). Selectively inhibiting the dipeptidyl peptidase activity of FAP using a chemical inhibitor (naphthalenecarboxy-Gly-boroPro) notably suppresses parallel matrix alignment and results in a randomly oriented matrix structure, suggesting that the enzymatic activity of FAP serves a decisive role in matrix remodeling (64).

Beyond remodeling the ECM to provide a physical scaffold for tumor growth, FAP+ CAFs promote angiogenesis to support the nutrient and oxygen supply (43,65). Positioned within the perivascular niche and establishing close spatial association with endothelial cells, FAP+ CAFs drive the formation of new blood vessels by secreting VEGF, which sustains the activation of canonical pro-angiogenic signaling pathways in endothelial cells (43). These matrix-remodeling and pro-angiogenic functions act synergistically to form the structural foundation of the tumor microenvironment.

FAP+ CAFs enhance the malignant properties of tumor cells. The regulation of malignant cells by FAP+ CAFs involves multiple signaling pathways and biological processes, as supported by both *in vitro* and *in vivo* experimental models (66-68). In both 3D spheroid assays and tumor-bearing mice, FAP+ CAFs notably promote the proliferation and invasion of ovarian cancer cells compared with their FAP- counterparts (39). Conditioned medium derived from FAP+ CAFs increases migration and invasion in hypopharyngeal squamous cell carcinoma cells (43), as well as the migration,

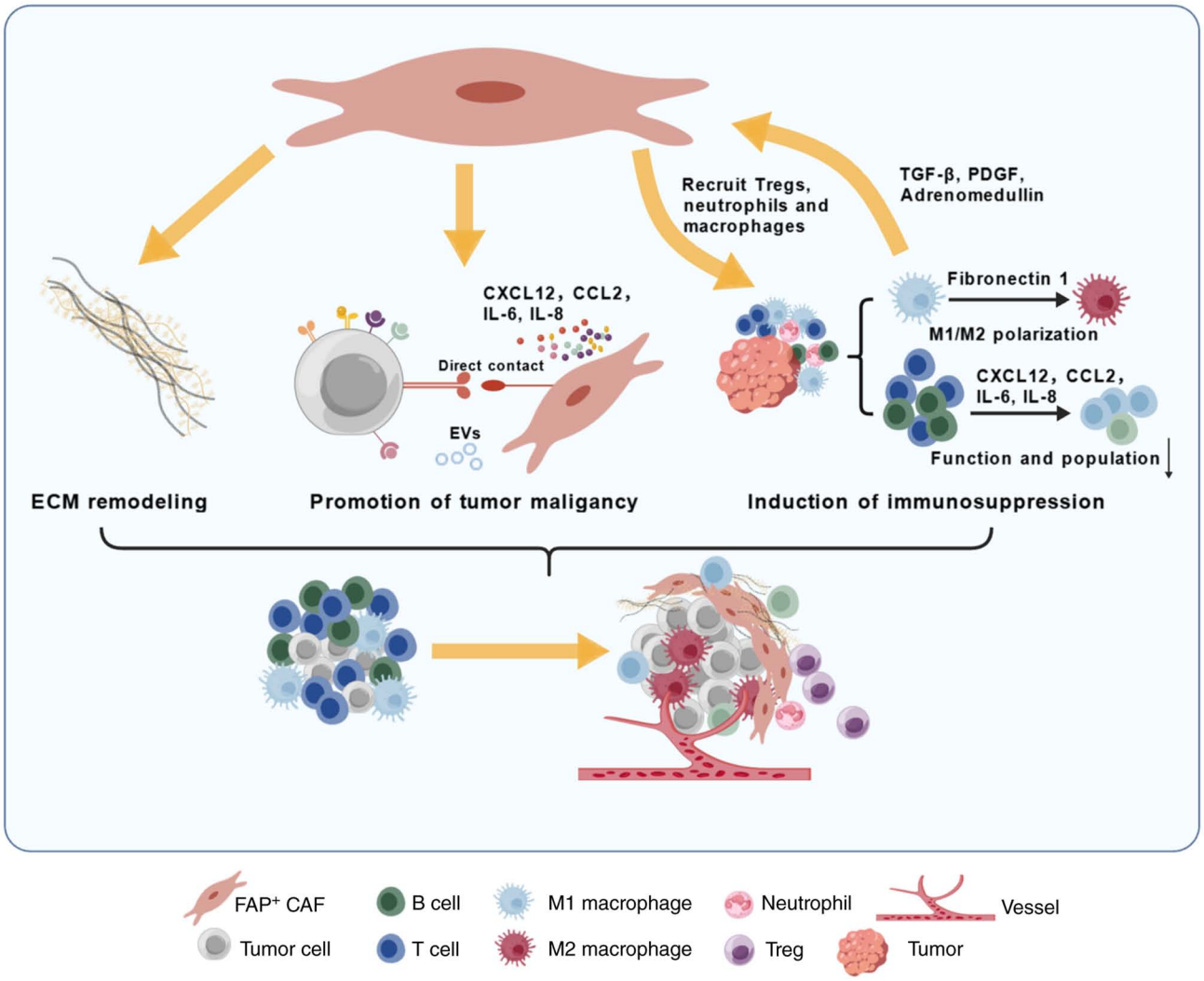

Figure 3. Key roles of FAP+ CAFs in promoting tumor progression. FAP+ CAFs shape a pro-tumorigenic microenvironment by orchestrating ECM remodeling, fostering an immunosuppressive niche through immune cell recruitment and polarization, and mediating communication with tumor cells via direct contact, EVs and cytokine signaling. FAP, fibroblast activation protein; CAF, cancer-associated fibroblast; ECM, extracellular matrix; EV, extracellular vesicle; Treg, regulatory T cell; PDGF, platelet-derived growth factor.

survival and drug resistance in gastric cancer cells (67). Indirect co-culture with FAP+ CAFs promotes proliferation in pancreatic cancer cells via inactivation of the cell cycle inhibitor retinoblastoma (68). These findings demonstrate that FAP+ CAFs secrete soluble factors that enhance malignant phenotypes in tumor cells. Some of these factors are cytokines that are highly expressed in FAP+ CAFs, including CCL2, IL-6, IL-8, CXCL12, growth factors (VEGF and insulin-like growth factor family members) and chemokines (69,70). For example, in esophageal squamous cell carcinoma, FAP+ CAFs activate the CXCL12/CXCR4 signaling pathway, which induces tumor cell proliferation, invasion and migration (71). In colon cancer, FAP+ CAFs exhibit aberrant activation of Wnt signaling, which leads to the enhanced secretion of fibroblast growth factor 20 (FGF20), a ligand that binds FGF receptor on cancer cells and activates PI3K/Akt signaling to promote tumor metastasis (72). FAP has been proposed to participate in regulating these cytokines (69) (Fig. 4). A notable positive association has been observed between FAP expression and the secretion of multiple cytokines, and suppressing FAP markedly decreases the secretion of IL-6, IL-8, and CCL2 (69). To the best of our knowledge, however, few studies have reported the potential mechanisms of FAP-mediated cytokine regulation in CAFs (73-75). FAP can promote the aggregation of the catalytic subunit of DNA-dependent protein kinase within lipid rafts, where it forms a stabilizing complex that increases Akt/NF-κB activation and may upregulate expression of downstream key cytokines such as CCL2, TNF-α and IL-8 (74,76). FAP can persistently activate STAT3 and facilitate its binding to the CCL2 promoter through a urokinase plasminogen activator receptor-dependent FAK/Src/JAK2 signaling cascade, thereby leading to increased CCL2 synthesis (7). Another potential mechanism for FAP-mediated cytokine secretion involves autocrine release of sFAP. sFAP can bind to enolase 1 on the cell membrane and activate the NF-κB pathway, which is known to regulate the secretion of multiple inflammatory cytokines including TNF-α, IL-6 and IL-8 (75). Abundant in the supernatant of FAP+ CAFs, sFAP directly activates the JAK2/STAT3 signaling pathway in neighboring cancer cells,

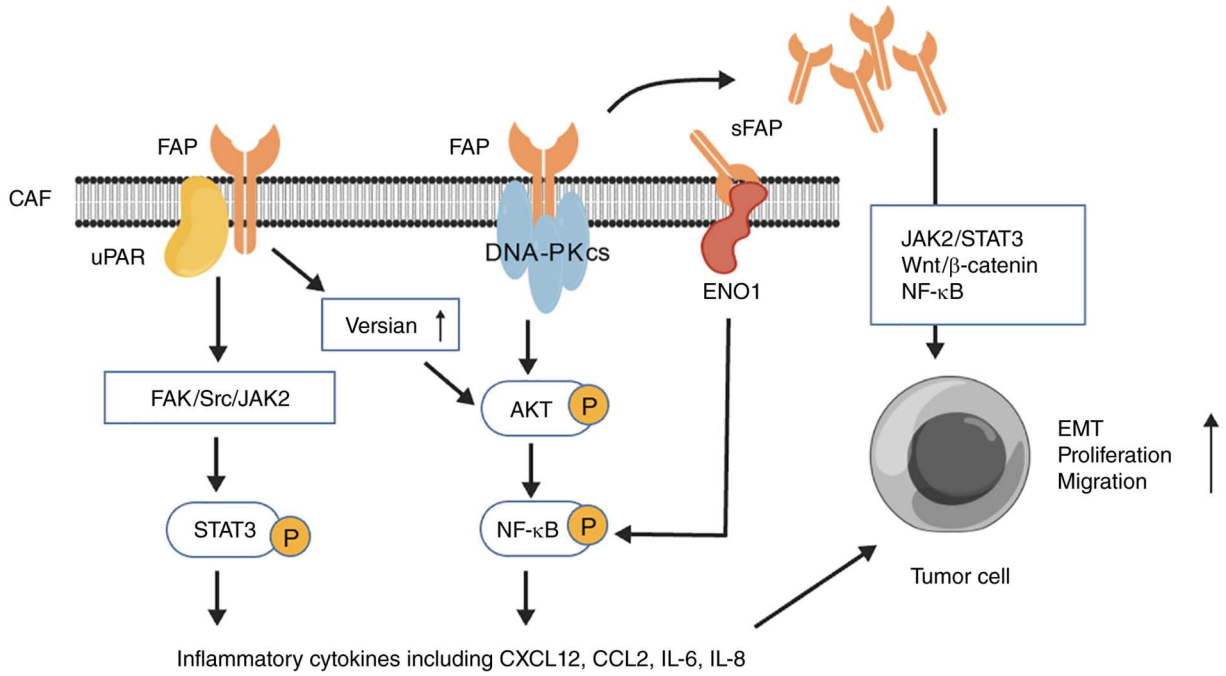

Figure 4. FAP-mediated signaling networks in CAFs promoting tumor malignancy. CAF-derived FAP (including sFAP) promotes tumor cell EMT, proliferation and migration by activating downstream signaling pathways and inducing inflammatory cytokine secretion. sFAP, soluble fibroblast activation protein; CAF, cancer-associated fibroblasts; uPAR, urokinase-type plasminogen activator receptor; DNA-PKcs, DNA-dependent protein kinase catalytic subunit; ENO, enolase; FAK, focal adhesion kinase; EMT, epithelial-mesenchymal transition.

leading to epithelial-mesenchymal transition (EMT) (49). In gastric cancer, sFAP activates the Wnt/β-catenin pathway in tumor cells in a dose-dependent manner, inducing EMT and enhancing cancer cell proliferation and migration (77).

In addition, other secreted factors highly expressed in FAP$^+$ CAFs have been implicated in the mediation of tumor cell phenotypes (30,78,79). For example, FAP upregulates the secretion of versican in FAP$^+$ CAFs, which activates the PI3K/AKT signaling pathway in bladder cancer cells to induce EMT (78). In ovarian cancer, secretory leukocyte protease inhibitor is highly expressed in FAP$^+$ CAFs and enhances the proliferation, migration, invasion and adhesion of ovarian cancer cells (30). Compared with FAP$^-$ CAFs, FAP$^+$ CAFs transfer a greater quantity of specific long non-coding RNAs via exosomes to esophageal squamous carcinoma cells, thereby enhancing radio-resistance by improving the DNA damage repair capacity of cancer cells (79).

FAP$^+$ CAFs as mediators of tumor immunosuppression. As aforementioned, the tendency of FAP$^+$ CAFs to localize at the tumor margin places them in proximity to immune cells recruited from distant sites. Through the secretion of bioactive factors or direct cell-cell contact, FAP$^+$ CAFs constitute a functionally immunosuppressive CAF subpopulation within the TME (80). Briefly, FAP$^+$ CAFs mediate immunosuppression through two primary mechanisms: Suppressing the abundance and/or function of anti-tumor immune cells such as effector T and natural killer (NK) cells (12,70) and recruiting immunosuppressive cell populations, including regulatory T cells (Tregs), myeloid-derived suppressor cells (MDSCs), neutrophils and tumor-associated macrophages (70,81).

T cells co-cultured with FAP$^+$ CAFs show decreased expression of granzyme B and IFN-γ, indicating a direct suppressive effect of FAP$^+$ CAFs on T cell function (67). FAP$^+$ CAFs can enhance the release of nitric oxide and thereby suppress the expansion of activated CD4$^+$ and CD8$^+$ T cells (82). In addition, numerous cytokines modulated by FAP expression are involved in immune regulation. For example, FAP$^+$ CAFs can promote the attraction of CD4$^+$CD25$^+$ T lymphocytes via CXCL12 and their differentiation into Tregs (83). IL-6 derived from FAP$^+$ CAFs enhance Treg survival and increase their proportion (26). FAP$^+$ CAFs induce MDSC recruitment into tumors through CCL2, which contributes to the reduced levels of functional molecules such as IL-2 and granzyme B in effector T cells (70). FAP is also involved in the polarization of macrophages from an anti-tumor (M1) to a pro-tumor (M2) phenotype (84). FAP promotes the secretion of fibronectin 1, triggering FAK/Akt/STAT3 signaling in macrophages and driving their polarization toward an immunosuppressive M2-like phenotype (13). These immunosuppressive cells recruited by FAP$^+$ CAFs not only directly suppress T cell function, but also form an interactive network with FAP$^+$ CAFs that continuously amplifies the immunosuppressive state within the TME. For example, upon arrival at the tumor area, tumor-associated macrophages can release paracrine factors such as TGF-β, PDGF and adrenomedullin to enhance the proliferation and tumor-promoting activity of FAP$^+$ CAFs (25). FAP elevates PD-L1 expression on CAFs, contributing to CD8$^+$ T cell exhaustion (85). Mechanistically, FAP enhances PD-L1 levels by inhibiting the degradation of STAT1, an upstream positive regulator of PD-L1 transcription (85). Moreover, FAP$^+$ CAFs produce more lactate than FAP$^-$ CAFs by upregulating LINC01711, which promotes lactate dehydrogenase A

Table III. Association between FAP+ CAFs and clinical variables across cancer types.

Cancer type	Clinical association	(Refs.)
Gastric	Advanced clinical stage; larger tumor size; poorer degree of differentiation; lymphovascular and nerve invasion; shorter PFS and OS	(84,122,131)
Colorectal	Shorter PFS and OS	(24,72,136)
Pancreatic	Histological differentiation; lymph nodes metastasis; shorter OS; tumor recurrence	(64,68,137)
Oral squamous cell carcinoma	Advanced clinical stage; lymph node metastasis; shorter OS	(118)
Esophageal squamous cell carcinoma	Lymph node metastasis; venous invasion; shorter OS and DFS	(69,79,138)
Ovarian	Advanced clinical stage; lymph node and omentum metastases; shorter PFS and OS	(30,39,74, 88,139)
Lung	Shorter OS	(31,140,141)
Bladder	Shorter OS and PFS	(90)
Liver	Advanced clinical stage; shorter OS; lymph node and distal metastasis	(25)

OS, overall survival; DFS, disease-free survival; PFS, progression-free survival.

phosphorylation, and monocarboxylate transporter 4 expression, which mediates lactate secretion (86). This metabolic feature creates an acidic TME that impairs $CD8^+$ T cell infiltration and function (86).

Although FAP may not directly regulate all of the aforementioned pro-tumorigenic or immunosuppressive factors and the observed co-expression may simply a coincidental signature of activated CAFs, FAP expression defines a CAF subset that serves a role in promoting tumor progression (71,79,86). As a critical mediator of FAP+ CAF-driven tumor promotion, FAP acts as an enzyme and modulates cytokine and signaling networks, thereby reshaping the stromal architecture and sustaining crosstalk with tumor cells and other components within the TME (54,85,87).

4. Association between FAP+ CAFs and clinicopathological variables

FAP+ CAFs are a key CAF subtype with growing clinical relevance (25,88,89). Accumulating evidence demonstrates that their abundance shows no significant association with basic demographic characteristics such as patient sex or age (77,90), whereas elevated infiltration of FAP+ CAFs indicates enhanced tumor malignancy and increased progression risk (24). Table III summarizes the association between FAP+ CAFs and clinicopathological features across cancer types.

Apart from their role in reflecting tumor progression, FAP+ CAFs demonstrate potential for dynamically monitoring treatment response. In patients with high-grade serous ovarian cancer, chemotherapy leads to a marked reduction in the relative proportion of FAP+ CAFs despite an overall increase in stromal content, indicating their specific vulnerability to cytotoxic agents (91). Parallel evidence emerges from immunotherapy studies: In colorectal cancer, enrichment of FAP+ CAFs is negatively associated with response to immune checkpoint inhibitors (ICBs) (21,24). Longitudinal changes in FAP+ CAF abundance during treatment are associated with both progression-free and overall survival (31). Collectively, these lines of evidence establish FAP+ CAFs as promising pan-cancer biomarkers for monitoring therapeutic efficacy across multiple treatment modalities.

5. FAP+ CAF targeting applications in diagnosis and therapeutics

FAP-targeting antibodies and inhibitors in cancer diagnosis and therapy. The distinct upregulation of FAP in malignant tissues compared with adjacent normal regions makes FAP an ideal target for tumor mapping. Concurrently, its key role in promoting tumor growth underscores its potential as a therapeutic target. These attributes have spurred development of FAP-directed ligands, antibodies and FAPIs for both diagnostic and therapeutic applications (92,93).

For precise tumor localization, FAP-targeting molecules are conjugated with fluorophores or radionuclides such as ^{68}Ga, ^{18}F and ^{89}Zr, enabling high-contrast visualization through advanced imaging techniques including PET and single photon emission CT (92,94). Several FAP-targeted imaging agents have been developed and show superior diagnostic performance in preclinical studies across a range of malignancies (95,96). For example, ^{89}Zr-labeled FAP IgG exhibits high uptake in both subcutaneous tumors and bone metastases, with detectable signals persisting for up to 72 h post-injection, thereby providing an extended window for PET/CT imaging (92). Intravenous administration of ^{68}Ga-labeled FAPI is well-tolerated, and its biodistribution is associated with FAP expression across cancer types (96). Notably, compared with ^{18}F-fluorodeoxyglucose, ^{68}Ga-FAPI displays superior tumor-to-background ratios and prolonged

retention across diverse tumor entities. Moreover, ^{68}Ga-FAPI PET/CT shows enhanced sensitivity in detecting early metastatic lesions (97). Nevertheless, certain types of benign disease may also exhibit high FAP expression, leading to non-specific FAPI uptake that may be misinterpreted as malignant lesions.

For therapeutic applications, FAPIs, antibodies and peptides are conjugated with therapeutic radionuclides such as ^{188}Re, ^{177}Lu, ^{225}Ac and ^{90}Y (98,99). The physical half-lives of these radionuclides align with the biological retention times of FAP-directed molecules in tumors, creating opportunities for targeted endoradiotherapy (100). For example, ^{177}Lu-labeled FAP-2286 (a FAP-binding peptide) exhibits favorable tumor uptake and symptom improvement in patients with rapidly progressing adenocarcinoma (98). In a subset of patients with advanced thyroid cancer and high FAP expression, ^{177}Lu-labeled FAPI derivatives markedly decrease bone and lymph node metastases (99). To date, FAP-targeted radioligand therapy has shown manageable side effects, including infrequent and reversible hematological toxicities as well as self-limiting headache and nausea (98). However, whether long-term therapy may cause adverse effects remains unclear, highlighting the need for additional data to assess its efficacy and safety.

FAP-targeted phototherapy is a treatment modality that can selectively eliminate localized lesions upon light exposure while avoiding systemic radiation exposure. FAP-IR700, a conjugate of FAP ligands with novel photosensitive dye IR700, can insert into adjacent lipid bilayers upon near-infrared light irradiation and causes cell membrane rupture, thereby selectively eliminating CAFs (101).

In the aforementioned therapeutic approaches, the structural design of FAP ligands is key as it directly affects pharmacokinetics, tumor uptake, clearance and therapeutic outcome. Modifying FAP ligands with chemical groups, such as amide bonds, can improve their binding affinity to cell surface FAP (93). Structural optimization of FAP-targeted pharmaceuticals, such as conjugation with albumin-binding domains or fatty acids, can enhance tumor uptake and prolong retention and therapeutic effect (99,102). Furthermore, enhancing selectivity is a key objective to mitigate off-target toxicity by minimizing the interaction of FAP-targeted drugs and normal cells with low FAP expression.

FAP$^+$ CAF elimination by chimeric antigen receptor (CAR) T therapy. FAP-CAR T cells drive a beneficial remodeling of TME through the dual mechanism of FAP$^+$ CAF depletion and T cell activation. Systemic administration of FAP-CAR T cells effectively suppresses tumor growth in mouse models of ovarian and lung cancer (103,104). In both human lung cancer xenografts and murine desmoplastic pancreatic tumors, selective depletion of FAP$^+$ CAFs by FAP-CAR T cells decreases the deposition of COL and glycosaminoglycans in the ECM, suppresses angiogenesis and notably inhibits tumor growth (105). A comparative study further revealed that FAP-CAR T cells exhibit superior anti-tumor efficacy relative to CAR T cells targeting a tumor-cell antigen (mesothelin) in pancreatic ductal adenocarcinoma models (106). Mechanistically, the elimination of FAP$^+$ CAFs inhibits tumor growth by disrupting the structural integrity of the desmoplastic matrix and enhancing the infiltration of endogenous CD8$^+$ T and NK cells (106).

Combined therapeutic opportunities. Although FAP-targeted therapy has shown efficacy in preclinical animal studies, its monotherapy offers limited clinical benefit (99,107,108). FAP-targeted monotherapy leads to increased FAP levels in some patients at late stages of treatment, suggesting the emergence of treatment resistance (109). A potential explanation is that FAP$^-$ CAFs survive during treatment and convert into and expand as FAP$^+$ CAFs under the influence of other factors in the TME. Recently, growing evidence indicates that combining FAP$^+$ CAF-targeting strategies with immunotherapy can produce combined effects and decrease drug resistance (110-112). In mouse models of colon cancer, FAP-targeted radiotherapy alone shows substantial activity, whereas its combination with anti-PD-L1 immunotherapy leads to complete eradication of all transplanted tumors (108,110). In gastric cancer, FAP-targeted therapy downregulates PD-L1 expression and upregulates immunostimulatory cytokines, including IL-2, IL-4, IL-10, IFN-γ and TNF-α, thereby sensitizing tumors to anti-PD-1 therapy (67). Furthermore, FAP-directed antibody-drug conjugates (ADCs) enhance the antitumor activity of ICBs by promoting the intratumoral infiltration of CD8$^+$ cytotoxic T cells (113). Additionally, combination of FAP-CAR T cells and anti-PD-1 therapy can exert a combined antitumor effect in pancreatic cancer by promoting endogenous CD8$^+$ T cell recruitment (114,115). FAP-targeting strategies also exhibit antitumor activity when combined with chemotherapeutic agents such as gemcitabine and paclitaxel (113,116). For example, although tumor regrowth may occur following FAP-targeted ADC monotherapy, its combination with gemcitabine induces more durable tumor regression (113). Moreover, the combination of a FAP-targeted radioligand with an IL-2 antibody produces stronger antitumor effects compared with either agent alone (117).

6. Conclusion

FAP is a classic surface marker of CAFs. FAP$^+$ CAFs defined by high FAP expression have drawn particular interest among CAF subsets (12,13,88). Their unique tumor distribution, fluctuating abundance and the dual enzymatic and non-enzymatic functions of their signature molecule FAP collectively underscore the key role of this subset in tumor progression. FAP engages other membrane proteins to participate in the activation of multiple intracellular signaling pathways as well as the regulation of cytokines and cellular proliferation and metabolism (87,118). Nevertheless, understanding of how FAP regulates CAF function and tumor progression remains incomplete. A challenge in understanding FAP$^+$ CAF biology is the instability of FAP expression under continuous *in vitro* culture conditions. Studies have reported a gradual downregulation of FAP expression in CAFs during extended culture periods (18,119). Using early-passage (passages 2-5) FAP$^+$ CAFs for experiments can minimize the impact of artificial culture conditions on cell characteristics (39). Alternatively, doxycycline treatment can be used to induce FAP expression in fibroblasts *in vitro,* which maintains stable expression for >10 days (64).

Despite FAP remaining a promising pan-cancer therapeutic target in clinical translation, its efficacy is limited in certain patients. This may be attributed to a low baseline proportion of FAP+ CAFs within the tumor tissue. Careful assessment of both tumoral and baseline FAP expression in normal tissues is of critical importance when selecting and implementing FAP-targeted therapeutic strategies. Understanding of the mechanisms regulating FAP production and its downstream signaling pathways may facilitate the identification of more effective targets for future FAP+ CAF-directed therapy.

Notably, studies have revealed that FAP+ CAFs exhibit functional preferences across different cancer types and tumor stages (32,72), suggesting that there may be other signals independent of FAP within FAP+ CAFs that participate in the regulation of tumor survival. Studies have aimed to classify FAP+ CAFs into more refined subsets through combinatorial biomarker profiling (120,121). For example, anthrax toxin receptor 1-positive FAP+ CAFs in ovarian cancer following chemotherapy can effectively suppress CD8+ T cell function through YAP1 signaling (91). In breast and gastric cancer, a FAP+ CD10+ G-protein-coupled receptor 77 (GPR77)+ CAF subpopulation is associated with the development of chemotherapy resistance (122). Thus, targeting FAP alone may be insufficient to suppress these FAP+ CAF subsets whose pro-tumorigenic functions rely on alternative parallel signaling pathways. Elucidating the mechanisms of such specialized subsets is key for the precise functional targeting of FAP+ CAFs, thereby enabling more durable tumor suppression.

Acknowledgements

Not applicable.

Funding

No funding was received.

Availability of data and materials

Not applicable.

Authors' contributions

ZT conceived the study and wrote the manuscript. ZZ constructed tables and figures. YW and JH reviewed and edited the manuscript. Data authentication is not applicable. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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