

Cancer-Associated Fibroblasts as Tumor Microenvironment Modifiers

Subjects: [Oncology](#)

Contributor: Kellen Wright , Thuc Ly , Matthew Kriet , Andras Czirok , Sufi Mary Thomas

Cancer-associated fibroblasts (CAFs) are stromal cells in the tumor microenvironment that are integral to cancer progression. Subtypes of CAFs across a variety of cancers have been revealed, and each play a different role in cancer progression or suppression. CAFs secrete signaling molecules that remodel the extracellular matrix, modulate immune responses and regulate cancer growth and metastasis.

extracellular matrix

tumor microenvironment

cancer-associated fibroblasts

1. Introduction

Cancer research for many years has focused on molecular perturbations in the tumor cells that contribute to progression and metastasis. The microenvironment surrounding the tumor cells plays an important role in progression. The tumor microenvironment (TME) is made up of non-cellular components including the extracellular matrix (ECM) and stromal cells. One of the most prominent cells in the TME are cancer-associated fibroblasts (CAFs), which can either impair or facilitate tumor growth and metastasis ^[1].

Historically discovered as a major component in connective tissues with a distinguished morphology, as elongated, spindle-like cells, fibroblasts are easily propagated in vitro ^[2]. Fibroblasts are normally quiescent; upon tissue injury, fibroblasts are activated to become myofibroblasts that proliferate and secrete growth factors, cytokines, and ECM proteins for wound healing ^[3]. Injured tissues release factors (e.g., TGF- β , PDGF, HGF, FGF2, inflammatory cytokines, metalloproteinases, and reactive oxygen species) that activate fibroblasts to acquire characteristics of smooth muscle cells, including the expression of α -smooth muscle actin (α -SMA) and contractile abilities ^{[4][5]}. As tumors resemble “wounds that do not heal”, they induce CAFs that form desmoplastic lesions of tumors, with α -SMA as one of the earliest described markers for CAFs ^[6]. Along with the advancement of molecular techniques, other markers of CAFs that correlate with poor patient survival (implicating the “protumor” perspective at a time) such as FSP1, FAP, vimentin, PDGFR-a, PDGFR-b, NG2, and CXCL12 have been identified ^{[7][8]}. However, none of these “markers” are exclusive to CAFs. In practice, CAFs are identified based on a combination of morphology, spindle shape, tissue position, and negative expression for epithelial cells (EpCAM), endothelial cells (CD31), immune cells (CD45), and pericytes (NG2) ^[9]. With the advancement of flow cytometry and single-cell RNA sequencing, it is evident that CAFs within tumor tissues are heterogenous in the transcriptional profile, and they are diverse across the cancer type as well.

2. CAFs Modulate the ECM Composition

The ECM serves as a scaffold for cells while regulating cellular activity and gene expression. The ECM is a composite of various molecules, such as proteins (e.g., collagens, elastin, proteoglycans, and glycoproteins), which include laminins and fibronectin. Each component can be detected by specialized cell-surface receptors, which collectively determine the material and transport properties of the tissue microenvironment. The composition of the ECM is tissue-, organ-, and species-specific [10]. The most basic classification of ECM types distinguishes the interstitial matrix from the basement membrane. The basement membrane is a denser collection of collagen IV and laminins that typically separate the epithelium from the underlying connective tissue, e.g., the epidermal layer from the dermis. The interstitial matrix comprises the three-dimensional mesh structure that typically consists of collagens I, III, and V, elastin, and fibronectin [11][12].

The ECM is a dynamic structure undergoing constant remodeling. Fibroblasts most commonly synthesize and secrete components of the ECM as well as extracellular enzymes that degrade portions of the ECM. In homeostasis, ECM production and degradation are in a balance that is responsive to changes in tissue function, including mechanical load bearing. Matrix metalloproteinases (MMPs) are the primary enzymes responsible for ECM degradation [13]. The activity of ECM-degrading enzymes is controlled by complex biological pathways, with tissue inhibitors of metalloproteinases (TIMPs) playing an important role [14]. Other enzymes are responsible for remodeling ECM, which includes plasmin, cathepsins, heparanases, and sulfatases [15].

ECM stiffness, a major marker of cancer's progressive and invasive potentials, is affected by the composition of the ECM [16]. The stiffness of the matrix impacts cancer cell proliferation, and aids in the resistance to treatment [17]. The yes-associated protein (YAP) and transcriptional coactivator with a PDZ-binding motif (TAZ) have been implicated in CAFs and poor prognosis in cancer. YAP/TAZ are oncoproteins that are active through the Hippo pathway [18]. Increased YAP/TAZ signaling results in the remodeling of the extracellular matrix and cell differentiation [19]. Additionally, the regulation of this pathway is largely controlled by physical cues in the surrounding microenvironment. Specifically, matrix stiffness has been shown to modulate the YAP/TAZ pathway. One mediator of YAP/TAZ remodeling, RAP2, is activated when ECM stiffness is low, inhibiting YAP/TAZ [20]. Calvo et al. demonstrated the activation of the YAP/TAZ pathway in CAFs cocultured with breast cancer cell lines [21]. YAP/TAZ-induced cytoskeletal regulators, including the actin-binding protein anillin (ANLN) and the actin-elongation regulator Diaphanous-Related Formin 3 (DIAPH3), contribute to matrix stiffening. Perturbation of YAP/TAZ rendered CAFs that were much less pro-tumorigenic. A positive feedback loop through activation of the YAP/TAZ pathway and increased matrix stiffness exacerbated the matrix stiffening. In another study, glycoprotein dickkopf-3 (DKK3) was identified as a mediator of CAF-regulated matrix stiffening. DKK3 acts by increasing the YAP/TAZ and Wnt/ β -catenin signaling pathways [22].

Collagens, which are the most abundant protein family in the human body, are deposited by fibroblasts and many other types of cells. The structure, stiffness, motility, and signaling potential of the ECM are all influenced by the balance of collagen fibers that make up the ECM [23]. Fibrillar collagen I, the most abundant collagen, is a fibril-forming collagen that is often secreted by fibroblasts. Collagen crosslinking is an essential part of ECM stiffening.

The lysyl oxidase (LOX) enzyme is responsible for the crosslinking of collagen I. The inhibition of LOX resulted in decreased stiffness and increased tumor latency [24]. In cancer types with increased CAF-expressed LOX, the ECM collagen I levels are higher. Breast cancer with CAFs expressing LOX has a higher rate of invasion and metastasis [25][26]. Similar observations were noted in ovarian, lung, HNSCC, esophageal adenocarcinoma, and colorectal cancers. An increased collagen fiber length was linked to a poor prognosis [27][28]. Li et al. demonstrated that CAF-secreted LOX at the metastatic niche is associated with a worse prognosis in gastric cancer patients [29]. Further, TGF- β signaling in CAFs induced the expression of LOX. The LOX inhibitor BAPN reduced the metastasis of gastric cancer to the liver.

ECM components may facilitate tumor suppression in some cases and can be tumor-promoting in others. For example, Brisson et al. demonstrated that murine mammary carcinoma was more aggressive and metastasized more often in the collagen III-deficient murine mammary cell line 4T1 [30][31]. However, collagen III was reported to facilitate cancer cell migration in prostate cancer [32]. The depletion of type V collagen reduced tumor growth in mammary carcinoma [33].

Type VI collagen is found to be upregulated specifically in CAFs in colorectal carcinoma (CRC) [34]. Other cancers that were reported to have highly expressed type VI collagen include melanoma, ovarian cancer, lung cancer, esophageal cancer, pancreatic cancer, breast cancer, and more. Col6a1^{-/-} mice with B16F10 melanoma allografts in the brain had decreased tumor proliferation compared to wild-type control mice due to reduced vasculature. Other effects of type VI collagen include the recruitment of macrophages, increases in inflammation, and angiogenesis [35].

In HNSCC, collagen XI α 1 (colXI α 1) was elevated in comparison to controls in tumor cells and stromal fibroblasts, and the knockdown of colXI α 1 restricted HNSCC cell proliferation in vitro. This illustrates a pro-tumor effect of type XI collagen [36][37]. Less is known about collagen types XXII and XXIV; however, increased mRNA expression in HNSCC is associated with metastasis and recurrence [38].

Tissue inhibitors of matrix metalloproteinases (TIMPs) are multi-faceted proteins that act downstream of multiple signaling pathways to inhibit MMPs [39]. TIMPs have been implicated in cancer progression and metastasis. For instance, CAF-secreted TIMP-1 initiates a STAT3 feedback loop that has been shown to play an integral part in breast cancer growth and migration [40].

MMPs are important players in ECM dynamics. MMP-2 is elevated in both CAFs and bladder cancer cell lines, which contributes to tumor growth [41]. Further, CAFs induce MMP-2 and -14 expression in cancer cells [42]. In gastric cancer, CAF-mediated signaling induces the expression of MMP-2/9, and TIMP-1/2 increases the tumor invasion by activating the JAK2/STAT3 pathway [43].

Fibronectin is a component of the ECM that is deposited by fibroblasts. In cancer, fibronectin is implicated in the invasion. Fibronectin is secreted by CAFs that are isolated from colon cancer patients at a higher rate than normal fibroblasts [44]. The depletion of fibronectin in CAFs through siRNA silencing reduced the cancer's ability to invade,

indicating that fibronectin is required for CAF-mediated tumor invasiveness. However, CAFs that are lacking in fibronectin retained their ability to apply mechanical force and organize the collagen network. Glentis et al. demonstrated that physical contact between CAFs and tumor cells was required to assist with invasion, and that this process was independent to MMP activity [45]. Using live imaging of CAFs moving along the basement membrane, they showed that CAFs widened holes in the basement membrane, thus allowing cancer cells to penetrate and invade.

In addition to modifying the entire surrounding tumor stroma, CAFs can remodel specific parts of the ECM, allowing for easier invasion. Reported by Gaggioli et al., CAFs lead invading cancer cells, leaving an invasion-friendly pathway in their wake [46]. These “tracks,” provide a permissive environment that allows for a more frequent and aggressive invasion. The tracks are characterized by “thick collagen bundles around their sides and an absence of matrix in their center,” and the deposition of fibronectin and tenascin-C. The presence of tumor cells is not required for track formation. Track formation is partly mediated by the Rho/ROCK pathway in CAFs, and inhibition of these pathways at several steps limits the amount of remodeling that is performed.

Using a simulated cancer environment, experiments showed that the migration of fibroblasts creates a permissive environment for tumor cells to follow. The migration of fibroblasts toward lymphatics is linked to an increasing concentration of TGF- β in the direction of movement. Tumor cells can also physically attach themselves to moving CAFs, allowing for the movement of tumor cells. This increased velocity leads to greater tumor aggressiveness [47]. Podoplanin, a glycoprotein, modulates track formation and invasiveness. Cancers with high podoplanin-positive CAF populations correlate with poor clinical outcomes. CAFs that express podoplanin also further invade the ECM in both in vitro and in vivo studies. Podoplanin acts via the Rho/ROCK signaling pathway [48]. In CAFs, the Rho/ROCK pathway modulates actomyosin contractility and is shown to be a requirement for force-mediated ECM remodeling [49].

Discoidin domain receptor 2 (DDR2), a fibrillar collagen receptor, is present on both tumor cells and CAFs [50]. Increased expression is related to tumor metastasis in breast cancer in mice, without affecting primary tumor growth. In CAFs, DDR2 expression is directly related to the ability of CAFs to remodel the ECM. The depletion of DDR2 in CAFs changed the resulting ECM to resemble an ECM produced by normal fibroblasts.

While the effect of CAFs on the ECM and surrounding cells is typically tumor-promoting, the heterogeneity of CAF populations allows for different pro-tumor effects, with some populations reported to restrict tumor growth [8]. α SMA+ fibroblasts, also known as myCAF_s in pancreatic cancer, have been recently shown to slow tumor progression in colorectal cancer. Reduction of α SMA+ CAFs in mouse models fostered a more immunosuppressive TME [51]. Other experiments have eliminated α SMA+, potentially targeting tumor-restraining CAFs and not tumor-promoting CAFs [52]. α SMA is not uniformly positive in all CAFs, and it has varying expression levels within α SMA+ CAFs [8]. Meflin, a protein present in some CAF populations, is essential for anti-tumor effects. The reduction of meflin in these populations resulted in a more aggressive pancreatic ductal adenocarcinoma (PDAC) course in mouse models [53]. The cancer-restraining properties of CAFs are not well understood. Future research into pro-

and anti-tumor properties and the heterogeneity of CAFs will allow an improved method of targeting the TME in cancer treatment.

3. CAF-Secreted Factors Facilitate Tumor Progression

CAFs adopt an activated phenotype that secretes several factors that facilitate tumor growth and metastasis. These factors can act in a paracrine manner: they bind to the cell surface receptors of nearby cells and trigger downstream molecular signaling pathways (**Table 1**).

Table 1. Signaling molecules and growth factors secreted by CAFs into the TME.

Factor	Receptor	Reference
TGF- β 1 and TGF- β 2	TGF- β R type I and II	[54][55][56][57][58][59][60]
IL-6	IL-6R	[61][62]
IL-8	CXCR1/2	[63][64]
MCP1 (CCL2)	CCR-2	[65][66][67]
HGF (SF)	c-Met	[68][69]
LIF	LIFR	[70][71]
SDF-1 (CXCL12)	CXCR4	[8][72]
CXCL1	CXCR2	[41][73][74]
FGF1, FGF2, and FGF9	FGFR, FGFR2, and FGFR9	[75][76]
CCL-5	CCR1, CCR3, and CCR5	[77]
IL-11	IL-11R	[77]

Both tumor and stromal cells in the microenvironment respond to CAF-secreted factors (**Figure 1**). Transforming growth factor- β (TGF- β), has wide-ranging effects on physiological processes as well as cancer [78]. It contributes toward tumor epithelial to mesenchymal transition (EMT) and invasiveness [58]. This cytokine is implicated in driving the formation of LRRC15+ CAFs [79]. Activated CAFs secrete TGF- β , leading to a positive feedback loop prompting the secretion of lysyl oxidase (LOX) enzymes from CAFs and other cells. Specifically, the secretion of LOX like-2, promotes collagen crosslinking, increasing the stiffness of the ECM in hepatocellular carcinoma (HCC) [57]. TGF- β also increases fibronectin synthesis, thus promoting a matrix-associated fibronectin assembly process called fibrillogenesis [56]. In addition, it also activates immune cells such as M2 macrophages, thus producing inflammation and the deposition of ECM components in the liver resulting in fibrosis [54]. In mammary tumors,

autocrine signaling of TGF- β in fibroblasts sustains the CAF phenotype. In addition, TGF- β along with stromal cell-derived factor 1 (SDF-1) facilitate the development of tumor-promoting CAFs [55].

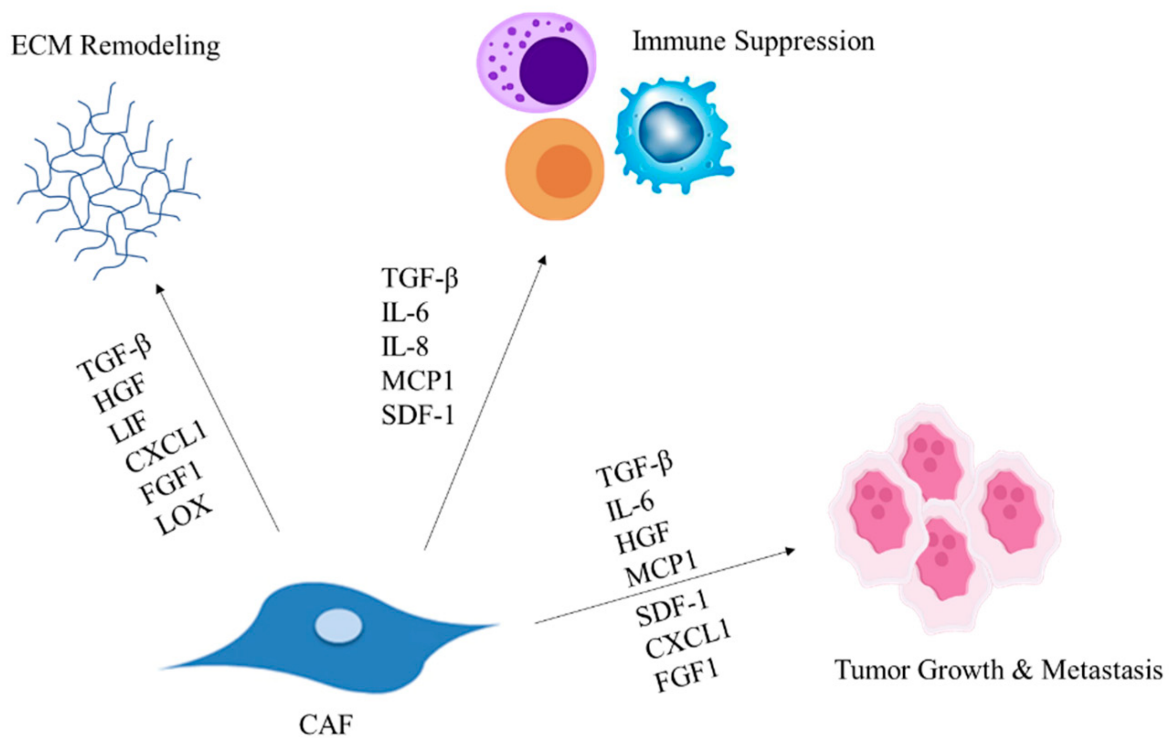


Figure 1. CAF factors influence pro-tumor processes. CAF-derived molecules TGF- β , HGF, LIF, CXCL1, and FGF1 impact ECM remodeling. Factors SDF-1, MCP1, IL-8, IL-6, and TGF- β modulate the immune system. TGF- β , IL-6, HGF, MCP1, SDF-1, CXCL1, and FGF1 impact tumor growth and metastasis.

In CRC, CAFs have been reported to secrete IL-6, which is a cytokine with pleiotropic activity including inflammation and angiogenesis. Tumor-derived IL-6 induces the vascular endothelial growth factor (VEGF) release from CAFs [62]. In pancreatic cancer, increased IL-6 expression was associated with an increased immunosuppressive stroma. A reduction in the amount of collagen in the ECM was noted with an interleukin 6 receptor (IL6R) antibody treatment [61]. IL-6 is shown to act through the STAT3 pathway [80]. Head and neck squamous cell carcinoma (HNSCC) tumors have an intricate mechanism of inducing a process called secretory autophagy in CAFs [81]. HNSCC-secreted FGF2 induces the STAT3-mediated transcription of SOX2, which in turn suppresses the expression of mTOR inducing secretory autophagy in CAFs. Several factors including IL-6 and IL-8 are secreted from CAFs into the tumor microenvironment.

The hepatocyte growth factor (HGF), also known as scatter factor, is secreted by CAFs in some cancers [82]. HGF contributes to desmoplasia as well as to the acidification of the TME through the regulation of tumor metabolism. In ovarian cancer cells, HGF secreted by CAFs increased the therapeutic resistance and cell proliferation [68]. In HNSCC, HGF induces glycolysis, which facilitates the secretion of tumor-derived lactate [4]. CAFs in turn, respond to HNSCC-released FGF2 to increase lactate uptake and mitochondrial oxidative phosphorylation. Inhibiting the HGF/c-Met pathway reduced HNSCC tumor growth [4][83].

The leukemia inhibitory factor (LIF) is another signaling molecule that is implicated in the remodeling of extracellular matrix. The tumor secreted LIF promotes CAF activation and the expression of LIF in fibroblasts [70]. Further, LIF regulates pro-invasive effects of CAFs on HNSCC through the regulation of actomyosin contractility, which is independent of α -SMA expression in CAFs. LIF also facilitates the pro-tumor effects of TGF- β and is correlated with a poor clinical prognosis.

The stromal cell-derived factor 1 (SDF-1), also known as C-X-C motif chemokine 12 (CXCL12), can facilitate macrophage recruitment during cancer progression. Inhibiting SDF-1 restricted macrophage migration at an even higher rate than MCP-1 inhibition in CAFs associated with breast cancer cells [65]. SDF-1 expression is a poor prognostic indicator in endometrial cancer. Working through the SDF-1/CXCR4 pathway, SDF-1 increased MMP-2/MMP-9 production and led to an increased tumor invasiveness [84]. Zhu et al. further investigated the pathways involving CXCL12 [85]. TWIST1 is a transcription factor that when overexpressed, leads to increased amounts of CXCL12. The knockdown of TWIST1 in CAFs limited the epithelial–mesenchymal transition (EMT) of esophageal cancer cells.

C-X-C motif chemokine ligand 1 (CXCL1) is highly expressed in HNSCC CAFs and is associated with poor survival. Further, CAF-conditioned media or CAF-secreted CXCL1 increased the tumor invasion [86]. This expanded invasive capacity is a result of the CXCL1-mediated increase in CAF-secreted MMP1.

In experiments with CRC, FGF1 expression by CAFs was increased alongside the activation of its receptor, FGFR3. When FGF1 expression was reduced, the migratory ability of the tumor cells was reduced. These FGF1-producing fibroblasts were determined to be FAP-positive CAFs [76]. In lung cancer, CAFs were shown to overexpress FGF2 and FGF9. These CAF populations secreted high levels of collagen and contributed to tumor aggressiveness [75]. FGF2 signaling activated pathways that led to the acquisition of a CAF phenotype [87].

Du et al. demonstrated that Hic-5, an intracellular protein expressed at higher levels in CAFs than normal fibroblasts, is associated with an increased lymph node metastasis. Specifically, experiments indicated that Hic-5 enhanced cell migration and invasion in esophageal cancer. Stromal components such as MMP-2 were altered in Hic-5 knockdown CAFs [88]. Similarly, palladin is an actin-binding protein product of CAFs that is indicated in stromal remodeling. Upregulated in CAFs in four different types of adenocarcinoma, it was hypothesized to impact tumor aggressiveness. Increased palladin expression in CAFs is associated with a poor prognostic outcome in colorectal cancer [34].

CAF interaction with the TME is not limited to secreted factors. CAFs secrete microvesicles as a key facilitator of cell–cell communication and tumor–stroma interaction. CAF-derived microvesicles mediate miRNA transfer to normal fibroblasts, leading to their transformation into CAFs in some instances. Exosomes are a subtype of microvesicles that are secreted by CAFs and contribute to tumorigenesis and metastasis when their contents are horizontally transferred. Chen et al. reported that exosomes released by CAFs promote breast cancer proliferation by transferring miR-500a-5p to cancer cells [89]. The horizontal transfer of miRNA by CAF-derived microvesicles may also contribute to therapy resistance [90]. Sansone et al. demonstrated that microvesicle-mediated miR-221

transfer increased hormonal therapy resistance (HTR) in a luminal breast cancer model [91]. A study by Zhang et al. demonstrated that CAF-derived exosomes transfer miR-522 to tumor cells, triggering ferroptosis inhibition, leading to tumor advancement and lowered susceptibility to chemotherapy [92]. Extracellular vesicles released by ovarian cancer cells can induce fibroblast differentiation into fibroblasts [93].

These findings establish that cell–cell communication is not restricted to growth factor secretion, but microvesicles and exosomes also play an important role through the transfer and exchange of miRNA and other biological molecules.

4. CAFs Modulate Immune Cell Recruitment Leading to Suppressed Immune Response

A major impact of CAFs on cancer progression is the communication and modulation of the immune system (Table 2). CAFs and monocytes share significant crosstalk and influence factors such as invasion and prognosis. CAFs are partly responsible for recruiting macrophages to the tissue stroma. As previously discussed, type VI collagen [35] and SDF-1 [65] are factors secreted by CAFs that aid in the recruitment of macrophages. Once recruited, CAFs also play a part in differentiating these macrophages into the M2 phenotype.

Once macrophages are differentiated into M2 macrophages, these cells are involved in pro-tumor activity. They are involved in phagocytosis, immune suppression, angiogenesis, and the alteration of the extracellular matrix. The polarized M2 macrophages continue to communicate with tumor cells, CAFs, and other immune cells to propagate invasion [94].

Experiments performed by Zhang et al. demonstrate that PDAC CAFs induce the differentiation of monocytes into M2 macrophages. Once in the TME, M2 macrophages contributed to pro-tumor effects such as cell growth and invasion [77]. Macrophages can also serve as an origin for CAFs, as reported by Chiu-Tsun Tang et al. [95]. Through Smad3 regulation, macrophages underwent macrophage–myofibroblast transition (MMT), furthering lung cancer progression.

In CRC, CAF-secreted IL-8 facilitated the recruitment of macrophages [63]. CAFs upregulate VCAM-1 expression in colorectal cancer cells, which promotes the adhesion of monocytes. Further, the IL-8/CXCR2 pathway regulates the polarization of monocytes into an M2 phenotype. Antibody-mediated neutralization of IL-8 reduced the chemotaxis of monocytes. Similar results were seen when danirixin, a CXCR2 antagonist, was administered.

Monocyte chemoattractant protein 1 (MCP1), also known as CCL2, secreted by CAFs, promotes HNSCC invasion and migration [66]. MCP1 is also active in recruiting monocytes to cancerous tissue. Blocking MCP1 reduced the recruitment of monocytes to breast tumors [65].

Table 2. Cancer-associated fibroblasts recruit pro-tumor immune cells while inhibiting recruitment of anti-tumor immune cells.

CAF Subtype	Factor	Effect	Cancer Type	Reference
eCAF	Macrophages	M2 polarization	GC	[96]
Not determined	Monocytes	Differentiation into macrophages and recruitment to tumors	CRC and breast	[65][66]
Not determined	Mast cells	Mast cell degranulation	GC	[97]
Not determined	Natural killer cells	Reduction in NK cytotoxicity	PDAC	[98]
Not determined	Neutrophils	Neutrophil chemotaxis	HCC	[99]
apCAF	Tregs	T-cell differentiation into Tregs	PDAC	[100]
High-CAF	Helper T cells	Reduced helper T population	HNSCC	[101]
apCAFs	Cytotoxic T cells	Suppression of cytotoxic T cells	PDAC	[102]

CAFs also regulate mast cells. In mouse models of peritoneal tumors, CXCL12 from CAFs was suppressed. This reduced mast cell migration and degranulation and reduced tumor fibrosis [97]. Natural killer (NK) cells, an important immune component responsible for eliminating tumor cells, interact with CAFs as tumors progress. In PDAC, CAFs suppress natural killer cells [98]. Neutrophils involved in the immune response to cancer are also affected by CAFs. In HCC, CAFs recruited neutrophils via chemotaxis and protected them against apoptosis [99]. Protection from apoptosis occurred via activation of the IL6-STAT3 in neutrophils. Neutrophil survival benefits tumor progression, as these neutrophils suppress the T-cell immune response against the cancer.

Stromal fibroblasts communicate with several types of T cells in the cancer environment, further modulating the immune response to cancer. One study involving pancreatic cancer identified apCAFs, a classification of CAFs expressing MHCII molecules. These apCAF directly ligated to CD4 T cells, inducing differentiation into Tregs [100].

In GC, CAFs categorized as high risk with the CAFs-score criteria developed by Mak et al. had a reduced amount of helper T cells [103]. Cytotoxic T cells expressing CD8 levels are often reduced in cancer, leading to a suppressed immune response. In esophageal cancer, cancer cells cultured with CAFs resulted in a reduction of CD8⁺ T cells and a more aggressive cancer. Blocking the IL-6 pathway of signaling in CAFs led to a restoration of CD8⁺ T cells and hindered tumor growth [104]. In single-cell RNA sequencing experiments with gastric cancer, iCAFs chemoattract T cells through the secretion of IL-6 and CXCL12 [96].

References

1. Knowles, L.M.; Stabile, L.P.; Egloff, A.M.; Rothstein, M.E.; Thomas, S.M.; Gubish, C.T.; Lerner, E.C.; Seethala, R.R.; Suzuki, S.; Quesnelle, K.M.; et al. Hgf and c-met participate in paracrine tumorigenic pathways in head and neck squamous cell cancer. *Clin. Cancer Res.* 2009, 15, 3740–3750.
2. Kalluri, R. The biology and function of fibroblasts in cancer. *Nat. Rev. Cancer* 2016, 16, 582–598.
3. Shinde, A.V.; Humeres, C.; Frangogiannis, N.G. The role of alpha-smooth muscle actin in fibroblast-mediated matrix contraction and remodeling. *Biochim. Biophys. Acta Mol. Basis Dis.* 2017, 1863, 298–309.
4. Kumar, D.; New, J.; Vishwakarma, V.; Joshi, R.; Enders, J.; Lin, F.; Dasari, S.; Gutierrez, W.R.; Leef, G.; Ponnurangam, S.; et al. Cancer-associated fibroblasts drive glycolysis in a targetable signaling loop implicated in head and neck squamous cell carcinoma progression. *Cancer Res.* 2018, 78, 3769–3782.
5. Kuzet, S.E.; Gaggioli, C. Fibroblast activation in cancer: When seed fertilizes soil. *Cell Tissue Res.* 2016, 365, 607–619.
6. Dvorak, H.F. Tumors: Wounds that do not heal-redux. *Cancer Immunol. Res.* 2015, 3, 1–11.
7. Gascard, P.; Tlsty, T.D. Carcinoma-associated fibroblasts: Orchestrating the composition of malignancy. *Genes Dev.* 2016, 30, 1002–1019.
8. Miyai, Y.; Esaki, N.; Takahashi, M.; Enomoto, A. Cancer-associated fibroblasts that restrain cancer progression: Hypotheses and perspectives. *Cancer Sci.* 2020, 111, 1047–1057.
9. Sahai, E.; Astsaturov, I.; Cukierman, E.; DeNardo, D.G.; Egeblad, M.; Evans, R.M.; Fearon, D.; Greten, F.R.; Hingorani, S.R.; Hunter, T.; et al. A framework for advancing our understanding of cancer-associated fibroblasts. *Nat. Rev. Cancer* 2020, 20, 174–186.
10. Muncie, J.M.; Weaver, V.M. The physical and biochemical properties of the extracellular matrix regulate cell fate. *Curr. Top Dev. Biol.* 2018, 130, 1–37.
11. Winkler, J.; Abisoye-Ogunniyan, A.; Metcalf, K.J.; Werb, Z. Concepts of extracellular matrix remodelling in tumour progression and metastasis. *Nat. Commun.* 2020, 11, 5120.
12. Nissen, N.I.; Karsdal, M.; Willumsen, N. Collagens and Cancer Associated Fibroblasts in the Reactive Stroma and Its Relation to Cancer Biology. *J. Exp. Clin. Cancer Res.* 2019, 38, 115.
13. Mittal, R.; Patel, A.P.; Debs, L.H.; Nguyen, D.; Patel, K.; Grati, M.; Mittal, J.; Yan, D.; Chapagain, P.; Liu, X.Z. Intricate functions of matrix metalloproteinases in physiological and pathological conditions. *J. Cell. Physiol.* 2016, 231, 2599–2621.
14. Jackson, H.W.; Defamie, V.; Waterhouse, P.; Khokha, R. Timps: Versatile extracellular regulators in cancer. *Nat. Rev. Cancer* 2017, 17, 38–53.

15. Bonnans, C.; Chou, J.; Werb, Z. Remodelling the extracellular matrix in development and disease. *Nat. Rev. Mol. Cell Biol.* 2014, 15, 786–801.
16. Acerbi, I.; Cassereau, L.; Dean, I.; Shi, Q.; Au, A.; Park, C.; Chen, Y.Y.; Liphardt, J.; Hwang, E.S.; Weaver, V.M. Human breast cancer invasion and aggression correlates with ecm stiffening and immune cell infiltration. *Integr. Biol. (Camb)* 2015, 7, 1120–1134.
17. Najafi, M.; Farhood, B.; Mortezaee, K. Extracellular matrix (ecm) stiffness and degradation as cancer drivers. *J. Cell. Biochem.* 2019, 120, 2782–2790.
18. Luo, J.; Yu, F.X. Gpcr-hippo signaling in cancer. *Cells* 2019, 8, 426.
19. Noguchi, S.; Saito, A.; Nagase, T. Yap/taz signaling as a molecular link between fibrosis and cancer. *Int. J. Mol. Sci.* 2018, 19, 3674.
20. Meng, Z.; Qiu, Y.; Lin, K.C.; Kumar, A.; Placone, J.K.; Fang, C.; Wang, K.C.; Lu, S.; Pan, M.; Hong, A.W.; et al. Rap2 mediates mechanoresponses of the hippo pathway. *Nature* 2018, 560, 655–660.
21. Calvo, F.; Ege, N.; Grande-Garcia, A.; Hooper, S.; Jenkins, R.P.; Chaudhry, S.I.; Harrington, K.; Williamson, P.; Moeendarbary, E.; Charras, G.; et al. Mechanotransduction and yap-dependent matrix remodelling is required for the generation and maintenance of cancer-associated fibroblasts. *Nat. Cell Biol.* 2013, 15, 637–646.
22. Ferrari, N.; Ranftl, R.; Chicherova, I.; Slaven, N.D.; Moeendarbary, E.; Farrugia, A.J.; Lam, M.; Semiannikova, M.; Westergaard, M.C.W.; Tchou, J.; et al. Dickkopf-3 links hsf1 and yap/taz signalling to control aggressive behaviours in cancer-associated fibroblasts. *Nat. Commun.* 2019, 10, 130.
23. Sorushanova, A.; Delgado, L.M.; Wu, Z.; Shologu, N.; Kshirsagar, A.; Raghunath, R.; Mullen, A.M.; Bayon, Y.; Pandit, A.; Raghunath, M.; et al. The collagen suprafamily: From biosynthesis to advanced biomaterial development. *Adv. Mater.* 2019, 31, e1801651.
24. Levental, K.R.; Yu, H.; Kass, L.; Lakins, J.N.; Egeblad, M.; Erler, J.T.; Fong, S.F.; Csiszar, K.; Giaccia, A.; Weninger, W.; et al. Matrix crosslinking forces tumor progression by enhancing integrin signaling. *Cell* 2009, 139, 891–906.
25. Liu, J.; Shen, J.X.; Wu, H.T.; Li, X.L.; Wen, X.F.; Du, C.W.; Zhang, G.J. Collagen 1a1 (col1a1) promotes metastasis of breast cancer and is a potential therapeutic target. *Discov. Med.* 2018, 25, 211–223.
26. Pickup, M.W.; Laklai, H.; Acerbi, I.; Owens, P.; Gorska, A.E.; Chytil, A.; Aakre, M.; Weaver, V.M.; Moses, H.L. Stromally derived lysyl oxidase promotes metastasis of transforming growth factor-beta-deficient mouse mammary carcinomas. *Cancer Res.* 2013, 73, 5336–5346.

27. Cordes, N.; Ney, M.; Beleites, T.; Aust, D.; Baretton, G.; Thames, H.; Baumann, M.; Krause, M.; Lock, S.; Appold, S. Retrospective investigation of the prognostic value of the beta1 integrin expression in patients with head and neck squamous cell carcinoma receiving primary radio(chemo)therapy. *PLoS ONE* 2018, 13, e0209479.
28. Hanley, C.J.; Noble, F.; Ward, M.; Bullock, M.; Drifka, C.; Mellone, M.; Manousopoulou, A.; Johnston, H.E.; Hayden, A.; Thirdborough, S.; et al. A subset of myofibroblastic cancer-associated fibroblasts regulate collagen fiber elongation, which is prognostic in multiple cancers. *Oncotarget* 2016, 7, 6159–6174.
29. Li, Q.; Zhu, C.C.; Ni, B.; Zhang, Z.Z.; Jiang, S.H.; Hu, L.P.; Wang, X.; Zhang, X.X.; Huang, P.Q.; Yang, Q.; et al. Lysyl oxidase promotes liver metastasis of gastric cancer via facilitating the reciprocal interactions between tumor cells and cancer associated fibroblasts. *EBioMedicine* 2019, 49, 157–171.
30. Brisson, B.K.; Mauldin, E.A.; Lei, W.; Vogel, L.K.; Power, A.M.; Lo, A.; Dopkin, D.; Khanna, C.; Wells, R.G.; Pure, E.; et al. Type iii collagen directs stromal organization and limits metastasis in a murine model of breast cancer. *Am. J. Pathol.* 2015, 185, 1471–1486.
31. Sun, X.; He, X.; Zhang, Y.; Hosaka, K.; Andersson, P.; Wu, J.; Wu, J.; Jing, X.; Du, Q.; Hui, X.; et al. Inflammatory cell-derived cxcl3 promotes pancreatic cancer metastasis through a novel myofibroblast-hijacked cancer escape mechanism. *Gut* 2022, 71, 129–147.
32. Graf, F.; Horn, P.; Ho, A.D.; Boutros, M.; Maercker, C. The extracellular matrix proteins type i collagen, type iii collagen, fibronectin, and laminin 421 stimulate migration of cancer cells. *FASEB J.* 2021, 35, e21692.
33. Huang, G.; Ge, G.; Izzi, V.; Greenspan, D.S. A3 chains of type v collagen regulate breast tumour growth via glypican-1. *Nat. Commun.* 2017, 8, 14351.
34. Garcia-Palmero, I.; Torres, S.; Bartolome, R.A.; Pelaez-Garcia, A.; Larriba, M.J.; Lopez-Lucendo, M.; Pena, C.; Escudero-Paniagua, B.; Munoz, A.; Casal, J.I. Twist1-induced activation of human fibroblasts promotes matrix stiffness by upregulating palladin and collagen alpha1(vi). *Oncogene* 2016, 35, 5224–5236.
35. Chen, P.; Cescon, M.; Bonaldo, P. Collagen vi in cancer and its biological mechanisms. *Trends Mol. Med.* 2013, 19, 410–417.
36. Raglow, Z.; Thomas, S.M. Tumor matrix protein collagen xi α 1 in cancer. *Cancer Lett.* 2015, 357, 448–453.
37. Sok, J.C.; Lee, J.A.; Dasari, S.; Joyce, S.; Contrucci, S.C.; Egloff, A.M.; Trevelline, B.K.; Joshi, R.; Kumari, N.; Grandis, J.R.; et al. Collagen type xi α 1 facilitates head and neck squamous cell cancer growth and invasion. *Br. J. Cancer* 2013, 109, 3049–3056.

38. Misawa, K.; Kanazawa, T.; Imai, A.; Endo, S.; Mochizuki, D.; Fukushima, H.; Misawa, Y.; Mineta, H. Prognostic value of type xxii and xxiv collagen mrna expression in head and neck cancer patients. *Mol. Clin. Oncol.* 2014, 2, 285–291.
39. Ries, C. Cytokine functions of timp-1. *Cell Mol. Life Sci.* 2014, 71, 659–672.
40. Dittmer, A.; Dittmer, J. A caf-fueled timp-1/cd63/itgb1/stat3 feedback loop promotes migration and growth of breast cancer cells. *Cancers* 2022, 14, 4983.
41. Miyake, M.; Hori, S.; Morizawa, Y.; Tatsumi, Y.; Nakai, Y.; Anai, S.; Torimoto, K.; Aoki, K.; Tanaka, N.; Shimada, K.; et al. Cxcl1-mediated interaction of cancer cells with tumor-associated macrophages and cancer-associated fibroblasts promotes tumor progression in human bladder cancer. *Neoplasia* 2016, 18, 636–646.
42. Li, Y.Y.; Zhou, C.X.; Gao, Y. Interaction between oral squamous cell carcinoma cells and fibroblasts through tgf- β 1 mediated by podoplanin. *Exp. Cell Res.* 2018, 369, 43–53.
43. Zhang, J.; Li, S.; Zhao, Y.; Ma, P.; Cao, Y.; Liu, C.; Zhang, X.; Wang, W.; Chen, L.; Li, Y. Cancer-associated fibroblasts promote the migration and invasion of gastric cancer cells via activating il-17a/jak2/stat3 signaling. *Ann. Transl. Med.* 2020, 8, 877.
44. Attieh, Y.; Clark, A.G.; Grass, C.; Richon, S.; Pocard, M.; Mariani, P.; Elkhatib, N.; Betz, T.; Gurchenkov, B.; Vignjevic, D.M. Cancer-associated fibroblasts lead tumor invasion through integrin- β 3-dependent fibronectin assembly. *J. Cell Biol.* 2017, 216, 3509–3520.
45. Glentis, A.; Oertle, P.; Mariani, P.; Chikina, A.; El Marjou, F.; Attieh, Y.; Zaccarini, F.; Lae, M.; Loew, D.; Dingli, F.; et al. Cancer-associated fibroblasts induce metalloprotease-independent cancer cell invasion of the basement membrane. *Nat. Commun.* 2017, 8, 924.
46. Gaggioli, C.; Hooper, S.; Hidalgo-Carcedo, C.; Grosse, R.; Marshall, J.F.; Harrington, K.; Sahai, E. Fibroblast-led collective invasion of carcinoma cells with differing roles for rhogtpases in leading and following cells. *Nat. Cell Biol.* 2007, 9, 1392–1400.
47. Waldeland, J.O.; Polacheck, W.J.; Evje, S. Collective tumor cell migration in the presence of fibroblasts. *J. Biomech.* 2020, 100, 109568.
48. Neri, S.; Ishii, G.; Hashimoto, H.; Kuwata, T.; Nagai, K.; Date, H.; Ochiai, A. Podoplanin-expressing cancer-associated fibroblasts lead and enhance the local invasion of cancer cells in lung adenocarcinoma. *Int. J. Cancer* 2015, 137, 784–796.
49. Sanz-Moreno, V.; Gaggioli, C.; Yeo, M.; Albregues, J.; Wallberg, F.; Viros, A.; Hooper, S.; Mitter, R.; Féral, C.C.; Cook, M.; et al. Rock and jak1 signaling cooperate to control actomyosin contractility in tumor cells and stroma. *Cancer Cell* 2011, 20, 229–245.
50. Corsa, C.A.; Brenot, A.; Grither, W.R.; Van Hove, S.; Loza, A.J.; Zhang, K.; Ponik, S.M.; Liu, Y.; DeNardo, D.G.; Eliceiri, K.W.; et al. The action of discoidin domain receptor 2 in basal tumor cells

- and stromal cancer-associated fibroblasts is critical for breast cancer metastasis. *Cell Rep.* 2016, 15, 2510–2523.
51. McAndrews, K.M.; Vazquez-Arreguin, K.; Kwak, C.; Sugimoto, H.; Zheng, X.; Li, B.; Kirtley, M.L.; LeBleu, V.S.; Kalluri, R. Alphasma(+) fibroblasts suppress lgr5(+) cancer stem cells and restrain colorectal cancer progression. *Oncogene* 2021, 40, 4440–4452.
 52. Sperb, N.; Tsesmelis, M.; Wirth, T. Crosstalk between tumor and stromal cells in pancreatic ductal adenocarcinoma. *Int. J. Mol. Sci* 2020, 21, 5486.
 53. Mizutani, Y.; Kobayashi, H.; Iida, T.; Asai, N.; Masamune, A.; Hara, A.; Esaki, N.; Ushida, K.; Mii, S.; Shiraki, Y.; et al. Meflin-positive cancer-associated fibroblasts inhibit pancreatic carcinogenesis. *Cancer Res.* 2019, 79, 5367–5381.
 54. Fabregat, I.; Caballero-Diaz, D. Transforming growth factor-beta-induced cell plasticity in liver fibrosis and hepatocarcinogenesis. *Front. Oncol.* 2018, 8, 357.
 55. Kojima, Y.; Acar, A.; Eaton, E.N.; Mellody, K.T.; Scheel, C.; Ben-Porath, I.; Onder, T.T.; Wang, Z.C.; Richardson, A.L.; Weinberg, R.A.; et al. Autocrine tgf-beta and stromal cell-derived factor-1 (sdf-1) signaling drives the evolution of tumor-promoting mammary stromal myofibroblasts. *Proc. Natl. Acad. Sci. USA* 2010, 107, 20009–20014.
 56. Varadaraj, A.; Jenkins, L.M.; Singh, P.; Chanda, A.; Snider, J.; Lee, N.Y.; Amsalem-Zafran, A.R.; Ehrlich, M.; Henis, Y.I.; Myhreye, K. Tgf-beta triggers rapid fibrillogenesis via a novel tbetarii-dependent fibronectin-trafficking mechanism. *Mol. Biol. Cell* 2017, 28, 1195–1207.
 57. Wong, C.C.; Tse, A.P.; Huang, Y.P.; Zhu, Y.T.; Chiu, D.K.; Lai, R.K.; Au, S.L.; Kai, A.K.; Lee, J.M.; Wei, L.L.; et al. Lysyl oxidase-like 2 is critical to tumor microenvironment and metastatic niche formation in hepatocellular carcinoma. *Hepatology* 2014, 60, 1645–1658.
 58. Yu, Y.; Xiao, C.H.; Tan, L.D.; Wang, Q.S.; Li, X.Q.; Feng, Y.M. Cancer-associated fibroblasts induce epithelial-mesenchymal transition of breast cancer cells through paracrine tgf-beta signalling. *Br. J. Cancer* 2014, 110, 724–732.
 59. Suzuki, J.; Aokage, K.; Neri, S.; Sakai, T.; Hashimoto, H.; Su, Y.; Yamazaki, S.; Nakamura, H.; Tane, K.; Miyoshi, T.; et al. Relationship between podoplanin-expressing cancer-associated fibroblasts and the immune microenvironment of early lung squamous cell carcinoma. *Lung Cancer* 2021, 153, 1–10.
 60. Chung, J.Y.; Chan, M.K.; Li, J.S.; Chan, A.S.; Tang, P.C.; Leung, K.T.; To, K.F.; Lan, H.Y.; Tang, P.M. Tgf-beta signaling: From tissue fibrosis to tumor microenvironment. *Int. J. Mol. Sci.* 2021, 22, 7575.
 61. Kesh, K.; Garrido, V.T.; Dosch, A.; Durden, B.; Gupta, V.K.; Sharma, N.S.; Lyle, M.; Nagathihalli, N.; Merchant, N.; Saluja, A.; et al. Stroma secreted il6 selects for “stem-like” population and alters

- pancreatic tumor microenvironment by reprogramming metabolic pathways. *Cell Death Dis.* 2020, 11, 967.
62. Nagasaki, T.; Hara, M.; Nakanishi, H.; Takahashi, H.; Sato, M.; Takeyama, H. Interleukin-6 released by colon cancer-associated fibroblasts is critical for tumour angiogenesis: Anti-interleukin-6 receptor antibody suppressed angiogenesis and inhibited tumour-stroma interaction. *Br. J. Cancer* 2014, 110, 469–478.
63. Zhang, R.; Qi, F.; Zhao, F.; Li, G.; Shao, S.; Zhang, X.; Yuan, L.; Feng, Y. Cancer-associated fibroblasts enhance tumor-associated macrophages enrichment and suppress nk cells function in colorectal cancer. *Cell Death Dis.* 2019, 10, 273.
64. Gu, J.; Li, X.; Zhao, L.; Yang, Y.; Xue, C.; Gao, Y.; Li, J.; Han, Q.; Sun, Z.; Bai, C.; et al. The role of pkm2 nuclear translocation in the constant activation of the nf-kappab signaling pathway in cancer-associated fibroblasts. *Cell Death Dis.* 2021, 12, 291.
65. Gok Yavuz, B.; Gunaydin, G.; Gedik, M.E.; Kosemehmetoglu, K.; Karakoc, D.; Ozgur, F.; Guc, D. Cancer associated fibroblasts sculpt tumour microenvironment by recruiting monocytes and inducing immunosuppressive pd-1+ tams. *Sci. Rep.* 2019, 9, 3172.
66. Min, A.; Zhu, C.; Wang, J.; Peng, S.; Shuai, C.; Gao, S.; Tang, Z.; Su, T. Focal adhesion kinase knockdown in carcinoma-associated fibroblasts inhibits oral squamous cell carcinoma metastasis via downregulating mcp-1/ccl2 expression. *J. Biochem. Mol. Toxicol.* 2015, 29, 70–76.
67. Sun, C.; Li, X.; Guo, E.; Li, N.; Zhou, B.; Lu, H.; Huang, J.; Xia, M.; Shan, W.; Wang, B.; et al. Mcp-1/ccr-2 axis in adipocytes and cancer cell respectively facilitates ovarian cancer peritoneal metastasis. *Oncogene* 2020, 39, 1681–1695.
68. Deying, W.; Feng, G.; Shumei, L.; Hui, Z.; Ming, L.; Hongqing, W. Caf-derived hgf promotes cell proliferation and drug resistance by up-regulating the c-met/pi3k/akt and grp78 signalling in ovarian cancer cells. *Biosci. Rep.* 2017, 37, BSR20160470.
69. Konstorum, A.; Lowengrub, J.S. Activation of the hgf/c-met axis in the tumor microenvironment: A multispecies model. *J. Theor. Biol.* 2018, 439, 86–99.
70. Albregues, J.; Bourget, I.; Pons, C.; Butet, V.; Hofman, P.; Tartare-Deckert, S.; Feral, C.C.; Meneguzzi, G.; Gaggioli, C. Lif mediates proinvasive activation of stromal fibroblasts in cancer. *Cell Rep.* 2014, 7, 1664–1678.
71. Shi, Y.; Gao, W.; Lytle, N.K.; Huang, P.; Yuan, X.; Dann, A.M.; Ridinger-Saison, M.; DelGiorno, K.E.; Antal, C.E.; Liang, G.; et al. Targeting lif-mediated paracrine interaction for pancreatic cancer therapy and monitoring. *Nature* 2019, 569, 131–135.
72. Wang, Y.; Lan, W.; Xu, M.; Song, J.; Mao, J.; Li, C.; Du, X.; Jiang, Y.; Li, E.; Zhang, R.; et al. Cancer-associated fibroblast-derived sdf-1 induces epithelial-mesenchymal transition of lung adenocarcinoma via cxcr4/beta-catenin/ppardelta signalling. *Cell Death Dis.* 2021, 12, 214.

73. Cheng, W.L.; Wang, C.S.; Huang, Y.H.; Tsai, M.M.; Liang, Y.; Lin, K.H. Overexpression of cxcl1 and its receptor cxcr2 promote tumor invasion in gastric cancer. *Ann. Oncol.* 2011, 22, 2267–2276.
74. Lefler, J.E.; MarElia-Bennett, C.B.; Thies, K.A.; Hildreth, B.E., 3rd; Sharma, S.M.; Pitarresi, J.R.; Han, L.; Everett, C.; Koivisto, C.; Cuitino, M.C.; et al. Stat3 in tumor fibroblasts promotes an immunosuppressive microenvironment in pancreatic cancer. *Life Sci. Alliance* 2022, 5, e202201460.
75. Hegab, A.E.; Ozaki, M.; Kameyama, N.; Gao, J.; Kagawa, S.; Yasuda, H.; Soejima, K.; Yin, Y.; Guzy, R.D.; Nakamura, Y.; et al. Effect of fgf/fgfr pathway blocking on lung adenocarcinoma and its cancer-associated fibroblasts. *J. Pathol.* 2019, 249, 193–205.
76. Henriksson, M.L.; Edin, S.; Dahlin, A.M.; Oldenborg, P.A.; Oberg, A.; Van Guelpen, B.; Rutegard, J.; Stenling, R.; Palmqvist, R. Colorectal cancer cells activate adjacent fibroblasts resulting in fgf1/fgfr3 signaling and increased invasion. *Am. J. Pathol.* 2011, 178, 1387–1394.
77. Zhang, A.; Qian, Y.; Ye, Z.; Chen, H.; Xie, H.; Zhou, L.; Shen, Y.; Zheng, S. Cancer-associated fibroblasts promote m2 polarization of macrophages in pancreatic ductal adenocarcinoma. *Cancer Med.* 2017, 6, 463–470.
78. Syed, V. Tgf-beta signaling in cancer. *J. Cell. Biochem.* 2016, 117, 1279–1287.
79. Krishnamurty, A.T.; Shyer, J.A.; Thai, M.; Gandham, V.; Buechler, M.B.; Yang, Y.A.; Pradhan, R.N.; Wang, A.W.; Sanchez, P.L.; Qu, Y.; et al. Lrrc15(+) myofibroblasts dictate the stromal setpoint to suppress tumour immunity. *Nature* 2022, 611, 148–154.
80. Heichler, C.; Scheibe, K.; Schmied, A.; Geppert, C.I.; Schmid, B.; Wirtz, S.; Thoma, O.M.; Kramer, V.; Waldner, M.J.; Buttner, C.; et al. Stat3 activation through il-6/il-11 in cancer-associated fibroblasts promotes colorectal tumour development and correlates with poor prognosis. *Gut* 2020, 69, 1269–1282.
81. New, J.; Arnold, L.; Ananth, M.; Alvi, S.; Thornton, M.; Werner, L.; Tawfik, O.; Dai, H.; Shnayder, Y.; Kakarala, K.; et al. Secretory autophagy in cancer-associated fibroblasts promotes head and neck cancer progression and offers a novel therapeutic target. *Cancer Res.* 2017, 77, 6679–6691.
82. Rizwani, W.; Allen, A.E.; Trevino, J.G. Hepatocyte growth factor from a clinical perspective: A pancreatic cancer challenge. *Cancers* 2015, 7, 1785–1805.
83. Kumar; Kandl, C.; Hamilton, C.D.; Shnayder, Y.; Tsue, T.T.; Kakarala, K.; Ledgerwood, L.; Sun, X.S.; Huang, H.J.; Girod, D.; et al. Mitigation of Tumor-Associated Fibroblast-Facilitated Head and Neck Cancer Progression with Anti-Hepatocyte Growth Factor Antibody Ficlaturumab. *JAMA Otolaryngol. Head Neck Surg.* 2015, 141, 1133–1139.
84. Teng, F.; Tian, W.Y.; Wang, Y.M.; Zhang, Y.F.; Guo, F.; Zhao, J.; Gao, C.; Xue, F.X. Cancer-Associated Fibroblasts Promote the Progression of Endometrial Cancer Via the Sdf-1/Cxcr4 Axis.

- J. Hematol. Oncol. 2016, 9, 8.
85. Zhu, X.; Han, S.; Wu, S.; Bai, Y.; Zhang, N.; Wei, L. Dual role of twist1 in cancer-associated fibroblasts and tumor cells promoted epithelial-mesenchymal transition of esophageal cancer. *Exp. Cell Res.* 2019, 375, 41–50.
 86. Wei, L.Y.; Lee, J.J.; Yeh, C.Y.; Yang, C.J.; Kok, S.H.; Ko, J.Y.; Tsai, F.C.; Chia, J.S. Reciprocal activation of cancer-associated fibroblasts and oral squamous carcinoma cells through cxcl1. *Oral Oncol.* 2019, 88, 115–123.
 87. Bordignon, P.; Bottoni, G.; Xu, X.; Popescu, A.S.; Truan, Z.; Guenova, E.; Kofler, L.; Jafari, P.; Ostano, P.; Rocken, M.; et al. Dualism of fgf and tgf-beta signaling in heterogeneous cancer-associated fibroblast activation with etv1 as a critical determinant. *Cell Rep.* 2019, 28, 2358–2372.e2356.
 88. Du, X.; Xu, Q.; Pan, D.; Xu, D.; Niu, B.; Hong, W.; Zhang, R.; Li, X.; Chen, S. Hic-5 in cancer-associated fibroblasts contributes to esophageal squamous cell carcinoma progression. *Cell Death Dis.* 2019, 10, 873.
 89. Chen, B.; Sang, Y.; Song, X.; Zhang, D.; Wang, L.; Zhao, W.; Liang, Y.; Zhang, N.; Yang, Q. Exosomal mir-500a-5p derived from cancer-associated fibroblasts promotes breast cancer cell proliferation and metastasis through targeting usp28. *Theranostics* 2021, 11, 3932–3947.
 90. Boelens, M.C.; Wu, T.J.; Nabet, B.Y.; Xu, B.; Qiu, Y.; Yoon, T.; Azzam, D.J.; Twyman-Saint Victor, C.; Wiemann, B.Z.; Ishwaran, H.; et al. Exosome transfer from stromal to breast cancer cells regulates therapy resistance pathways. *Cell* 2014, 159, 499–513.
 91. Sansone, P.; Berishaj, M.; Rajasekhar, V.K.; Ceccarelli, C.; Chang, Q.; Strillacci, A.; Savini, C.; Shapiro, L.; Bowman, R.L.; Mastroleo, C.; et al. Evolution of cancer stem-like cells in endocrine-resistant metastatic breast cancers is mediated by stromal microvesicles. *Cancer Res.* 2017, 77, 1927–1941.
 92. Zhang, H.; Deng, T.; Liu, R.; Ning, T.; Yang, H.; Liu, D.; Zhang, Q.; Lin, D.; Ge, S.; Bai, M.; et al. Caf secreted mir-522 suppresses ferroptosis and promotes acquired chemo-resistance in gastric cancer. *Mol. Cancer* 2020, 19, 43.
 93. Giusti, I.; Di Francesco, M.; Poppa, G.; Esposito, L.; D'Ascenzo, S.; Dolo, V. Tumor-derived extracellular vesicles activate normal human fibroblasts to a cancer-associated fibroblast-like phenotype, sustaining a pro-tumorigenic microenvironment. *Front. Oncol.* 2022, 12, 839880.
 94. Najafi, M.; Hashemi Goradel, N.; Farhood, B.; Salehi, E.; Nashtaei, M.S.; Khanlarkhani, N.; Khezri, Z.; Majidpoor, J.; Abouzaripour, M.; Habibi, M.; et al. Macrophage polarity in cancer: A review. *J. Cell. Biochem.* 2019, 120, 2756–2765.
 95. Tang, P.C.; Chung, J.Y.; Xue, V.W.; Xiao, J.; Meng, X.M.; Huang, X.R.; Zhou, S.; Chan, A.S.; Tsang, A.C.; Cheng, A.S.; et al. Smad3 promotes cancer-associated fibroblasts generation via

- macrophage-myofibroblast transition. *Adv. Sci.* 2022, 9, e2101235.
96. Li, X.; Sun, Z.; Peng, G.; Xiao, Y.; Guo, J.; Wu, B.; Li, X.; Zhou, W.; Li, J.; Li, Z.; et al. Single-cell rna sequencing reveals a pro-invasive cancer-associated fibroblast subgroup associated with poor clinical outcomes in patients with gastric cancer. *Theranostics* 2022, 12, 620–638.
 97. Nakamura, Y.; Kinoshita, J.; Yamaguchi, T.; Aoki, T.; Saito, H.; Hamabe-Horiike, T.; Harada, S.; Nomura, S.; Inaki, N.; Fushida, S. Crosstalk between cancer-associated fibroblasts and immune cells in peritoneal metastasis: Inhibition in the migration of m2 macrophages and mast cells by tranilast. *Gastric Cancer* 2022, 25, 515–526.
 98. Huang, Q.; Huang, M.; Meng, F.; Sun, R. Activated pancreatic stellate cells inhibit nk cell function in the human pancreatic cancer microenvironment. *Cell Mol. Immunol.* 2019, 16, 87–89.
 99. Cheng, Y.; Li, H.; Deng, Y.; Tai, Y.; Zeng, K.; Zhang, Y.; Liu, W.; Zhang, Q.; Yang, Y. Cancer-associated fibroblasts induce pdl1+ neutrophils through the il6-stat3 pathway that foster immune suppression in hepatocellular carcinoma. *Cell Death Dis.* 2018, 9, 422.
 100. Huang, H.; Wang, Z.; Zhang, Y.; Pradhan, R.N.; Ganguly, D.; Chandra, R.; Murimwa, G.; Wright, S.; Gu, X.; Maddipati, R.; et al. Mesothelial cell-derived antigen-presenting cancer-associated fibroblasts induce expansion of regulatory t cells in pancreatic cancer. *Cancer Cell.* 2022, 40, 656–673.e657.
 101. Yang, Y.; Ma, B.; Han, L.; Xu, W.; Du, X.; Wei, W.; Liao, T.; Ji, Q.; Qu, N.; Wang, Y. Integrated single-cell and bulk rna sequencing analyses reveal a prognostic signature of cancer-associated fibroblasts in head and neck squamous cell carcinoma. *Front. Genet.* 2022, 13, 1028469.
 102. Elyada, E.; Bolisetty, M.; Laise, P.; Flynn, W.F.; Courtois, E.T.; Burkhart, R.A.; Teinor, J.A.; Belleau, P.; Biffi, G.; Lucito, M.S.; et al. Cross-species single-cell analysis of pancreatic ductal adenocarcinoma reveals antigen-presenting cancer-associated fibroblasts. *Cancer Discov.* 2019, 9, 1102–1123.
 103. Mak, T.K.; Li, X.; Huang, H.; Wu, K.; Huang, Z.; He, Y.; Zhang, C. The cancer-associated fibroblast-related signature predicts prognosis and indicates immune microenvironment infiltration in gastric cancer. *Front. Immunol.* 2022, 13, 951214.
 104. Kato, T.; Noma, K.; Ohara, T.; Kashima, H.; Katsura, Y.; Sato, H.; Komoto, S.; Katsube, R.; Ninomiya, T.; Tazawa, H.; et al. Cancer-associated fibroblasts affect intratumoral cd8(+) and foxp3(+) t cells via il6 in the tumor microenvironment. *Clin. Cancer Res.* 2018, 24, 4820–4833.

Retrieved from <https://encyclopedia.pub/entry/history/show/96558>