Review

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The evolving relationship of wound healing and tumor stroma

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The stroma in solid tumors contains a variety of cellular phenotypes and signaling pathways associated with wound healing, leading to the concept that a tumor behaves as a wound that does not heal. Similarities between tumors and healing wounds include fibroblast recruitment and activation, extracellular matrix (ECM) component deposition, infiltration of immune cells, neovascularization, and cellular lineage plasticity. However, unlike a wound that heals, the edges of a tumor are constantly expanding. Cell migration occurs both inward and outward as the tumor proliferates and invades adjacent tissues, often disregarding organ boundaries. The focus of our review is cancer associated fibroblast (CAF) cellular heterogeneity and plasticity and the acellular matrix components that accompany these cells. We explore how similarities and differences between healing wounds and tumor stroma continue to evolve as research progresses, shedding light on possible therapeutic targets that can result in innovative stromal-based treatments for cancer.

Introduction

Tumors are composed of transformed, cancer cells along with nontransformed stroma, a heterogeneous microenvironment composed of cancer associated fibroblasts (CAFs) (also known as tumor stromal fibroblasts), extracellular matrix (ECM) components, immune cells, blood vessels, and lymphatics. The stroma is critical for neoplastic proliferation. Moreover, we are beginning to appreciate the breadth of complex cellular interactions that occur in the tumor microenvironment (TME). The extent to which these findings differ in the wound healing process is beginning to be elucidated.

Malignant tumor progression relies on the TME, which promotes cancer cell growth by inducing leaky vasculature, cell migration, and angiogenesis. More than 30 years ago, Dvorak described the connection between the TME and wound healing, proposing a model in which tumor stroma forms through abnormal activation of wound healing pathways (1). Both the wound healing and TME rely on changes in ECM deposition that promote epithelial-mesenchymal transition (EMT) and increase motility of both fibroblasts and tumor cells. This dynamic environment is driven by plasticity in local cells that are activated in response to stress transiently during the wound healing process and indefinitely in cancer (2).

Each step of the intricate processes of wound healing and tumor development requires the interaction of fibroblasts and associated ECM components (3, 4). The first stage of wound healing is hemostasis, in which platelets arrest bleeding and form a clot at the site of injury, which transforms to fibrin. Fibrin, along with vitronectin and fibronectin, form early matrix, and fibroblasts are recruited to the wound. Subsequently, neutrophils are recruited and release cytokines (Figure 1A), inducing the inflammatory stage of wound healing. Fibroblasts are activated in the wound site and deposit ECM components such as collagen III. Macrophages are recruited and clear devitalized tissue and debris from the wound site. Keratinocytes migrate superficially to cover the wound, and new blood vessels extend to the wound bed (Figure 1B). Lastly, in the remodeling stage, fibroblasts facilitate wound contraction, collagen I replaces collagen III, and the ECM is remodeled with the help of proteases and other enzymes to form a mature scar. Some nerve regeneration occurs and new blood vessels are pruned (Figure 1C). In each of these phases, fibroblasts play a key role orchestrating the healing process.

In tumors, fibroblasts are also crucial for tumor progression, which can also be organized into analogous stages (4). When neoplasia begins, fibroblasts are recruited to the site. As the transformed cells multiply, the fibroblasts are activated and incorporated into the tumor. These CAFs produce dysregulated ECM proteins and proteases, forming a scaffold for the cancer cells to continue proliferation. Collagen stiffening and linear-
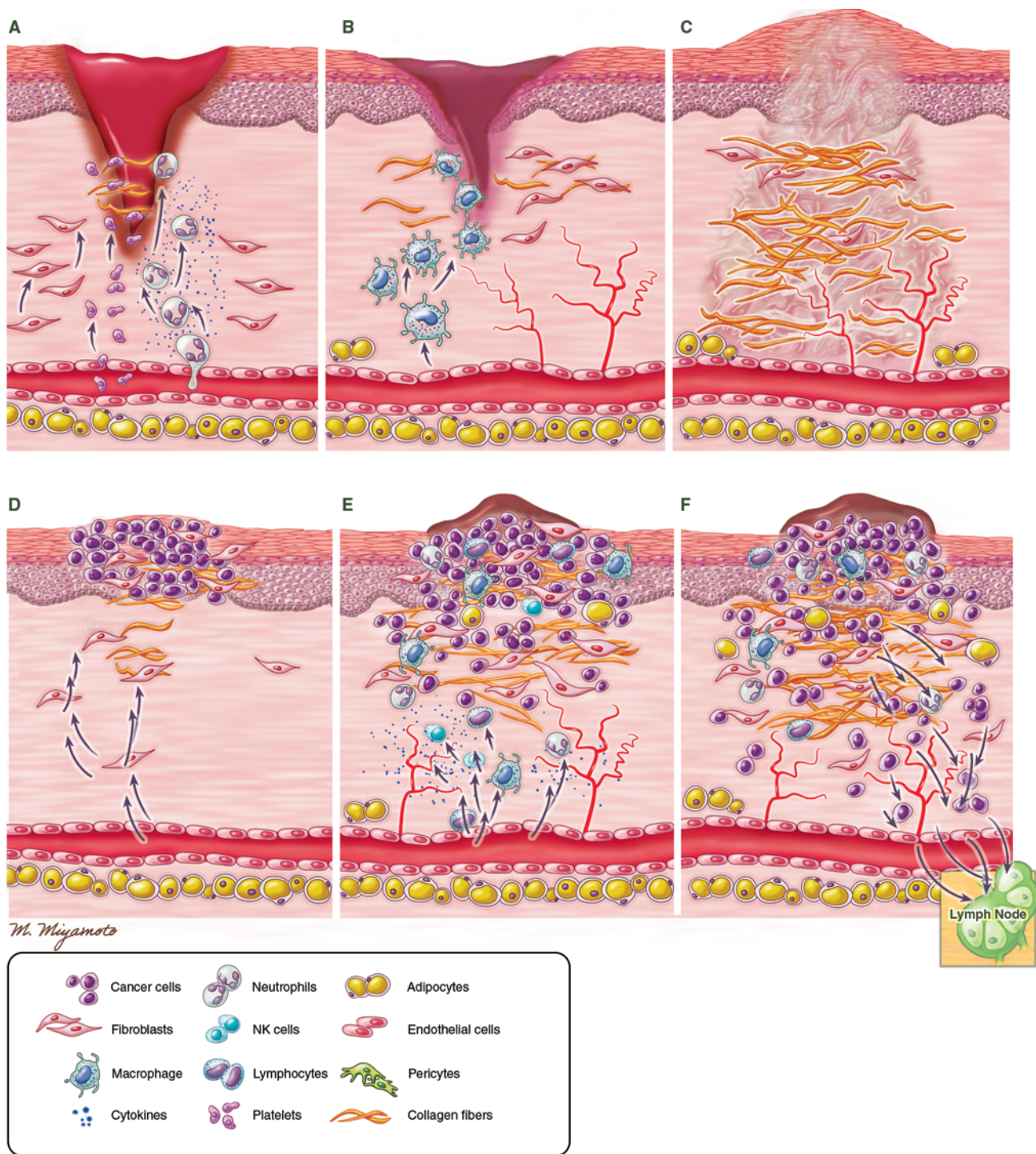
Figure 1. Comparative models of wound healing and tumor stroma. (**A**) The first phase of wound healing involves hemostasis; platelets form clot at the injury site, which transforms to fibrin. Fibrin, vitronectin, and fibronectin form early matrix. Neutrophils migrate to the wound and cytokines are released. Fibroblasts are recruited to the wound. (**B**) During the proliferation phase of wound healing, macrophages are recruited to clear dead tissue and debris. Keratinocytes migrate to cover the superficial wound area. New blood vessels form in the wound bed. Fibroblasts are activated in the wound and begin to deposit new ECM. (**C**) During the remodeling phase of wound healing, wound contraction occurs, collagen III is replaced by collagen I, and the ECM is remodeled by proteases and other enzymes. Nerve regeneration progresses and new vessels are pruned. (**D**) When neoplasia is first initiated, fibroblasts are recruited to the tumor site, activated, and incorporated. Production of dysregulated ECM proteins and proteases is stimulated, forming a scaffold for tumor proliferation. (**E**) As the tumor grows, the epithelium can be eroded away by cells expanding from below, causing ulceration at the skin edge of the tumor. VEGF and other signaling molecules induce neovascularization. Inflammatory cells are recruited to the TME and release cytokines. CAFs can adapt to tolerate and even participate in many of these features. Adipose cells also form a component of the tumor stroma. (**F**) The abnormal ECM is protumorigenic and proangiogenic. The tumor vasculature is leaky, which can allow metastases to distant sites. Tumor cells are also cleared by lymphatics and can permit lymphatic metastases. Illustrated by Mao Miyamoto.

ization by lysyl oxidase (LOX) characterize this dysfunctional ECM, which is firmer than surrounding tissues similar to a scar. The abnormal ECM is both protumorigenic and proangiogenic. The new tumor vasculature is leaky, which can allow hematogenous metastases to distant sites. Inflammatory cells are recruited to the tumor stroma and release cytokines. Immune infiltration is regulated by the leaky nature of the new vessels. Desmoplasia, a local fibrotic reaction associated with solid tumors, results in increased connective tissue. Cancer cells cause the TME to have a low pH and hypoxia, secondary to the Warburg effect. CAFs can adapt to tolerate and even participate in many of these features. Cancer cells can be cleared by local lymphatics, which drain to lymph nodes, initiating lymph node metastases in many tumor types. Epithelial cancer cells may undergo EMT and invade through the basement membrane, allowing hematogenous dissemination (4) (Figure 1, D–F). Here, we focus on how CAFs in tumor proliferation relate to wound healing.

Fibroblasts in solid tumors and cutaneous wounds

Fibroblasts are a dominant cell type involved in both wound healing (Figure 1, A–C) and tumor stroma (Figures 1, D–F). Fibroblasts are critical for tissue repair after injury and are involved in wound contraction, deposition of granulation tissue, production of ECM components, and tissue remodeling. In tumors, fibroblasts influence the microenvironment through direct contact with cancer cells and paracrine signaling, regulate the immune response to neoplasia, deposit diverse ECM components, stimulate neoangiogenesis (5), and provide a scaffold for tumor progression. Fibroblasts are known to have both tumor-promoting and tumor-inhibiting roles (6). In wound healing, equivalent fibroblasts are also called activated myofibroblasts, which highlights the transition these cells undergo from a resting, quiescent state to an activated form after tissue injury. The "myo-" prefix emphasizes the expression of α-smooth muscle actin (α-SMA), which is associated with these cells in both tumor and wounds (7–9).

Fibroblast activation. In homeostatic tissue, quiescent fibroblasts are spindle-shaped cells (6). Expression of fibroblast specific protein 1 (FSP-1) and α1β1 integrin are associated with quiescent fibroblasts in mice (10, 11). When a wound occurs or neoplasia is initiated, fibroblasts are recruited and activated in the microenvironment. Factors known to be involved in activating fibroblasts in both wound healing and tumor stroma include TGF-β signaling (7), PDGF (12), FGF2 (13, 14), HGF, IGF, connective tissue growth factor (CTGF), Wnt signaling (15, 16), integrin expression (17), and cell-cell interactions (Figure 2). In wound healing, TGF-β1, via the SMAD-4 pathway, stimulates wound healing activities including wound contraction by fibroblasts and ECM component deposition, as well as immune cell recruitment, angiogenesis, and keratinocyte migration via integrins (18). TGF-β2 shares similar roles to TGF-β1 and is involved in stimulating ECM deposition, while TGF-β3 is involved in regulating TGF-β1 and decreasing collagen I deposition and scar formation (18).

In the tumor context, PDGF, through its primary effector osteopontin, is specifically involved in recruitment, activation, and phenotypic remodeling of CAFs (19). Local recruitment of fibroblasts by chemokines also contributes to fibroblast activation in both wound healing and tumor proliferation. An example of CAF activation occurs during the development of skin cancer: Melanoma cells secrete TGF-β, PDGF, FGF2, and IL-8, which act in a paracrine manner to stimulate fibroblast activation and proliferation (19). Specifically, when melanocytes are transformed, PDGF signaling (20) simulates Snail upregulation (21), which causes downregulation of melanoma cell E-cadherin expression, allowing them to interact with fibroblasts more directly. This interaction is mediated by N-cadherin and connexins (22). Epigenetic modification, specifically aberrant DNA methylation, also drives fibroblast activation (2, 23).

Once activated, fibroblasts acquire different morphology than their quiescent counterparts and shift to a migratory phenotype. This change promotes wound healing, but also facilitates tumor proliferation (24). There is a common CAF gene expression signature that aligns with the wound healing response, and is predictive of prognosis in human cancer (25). When normal wound healing is complete, activated fibroblasts are culled, either via apoptosis (26) or a transition back to a resting state. In tumors, fibroblast activation is never turned off.

Fibroblast phenotypic and functional heterogeneity. There is significant heterogeneity in fibroblast cell surface marker and protein expression in postinjury repair and neoplastic proliferation (6). For example, α-SMA expression is primarily associated with activated fibroblasts (27) but is also expressed by tissue-resident fibroblasts (28), smooth muscle cells, and pericytes (29). Some cancer stromal fibroblasts express PDGFRα as well as or instead of α-SMA (30). FSP1 is primarily associated with quiescent fibroblasts but is also expressed by CAFs and identifies a unique cohort of CAFs in mice, which is independent from cells expressing α-SMA (31). Fibroblasts expressing the cell surface marker CD26
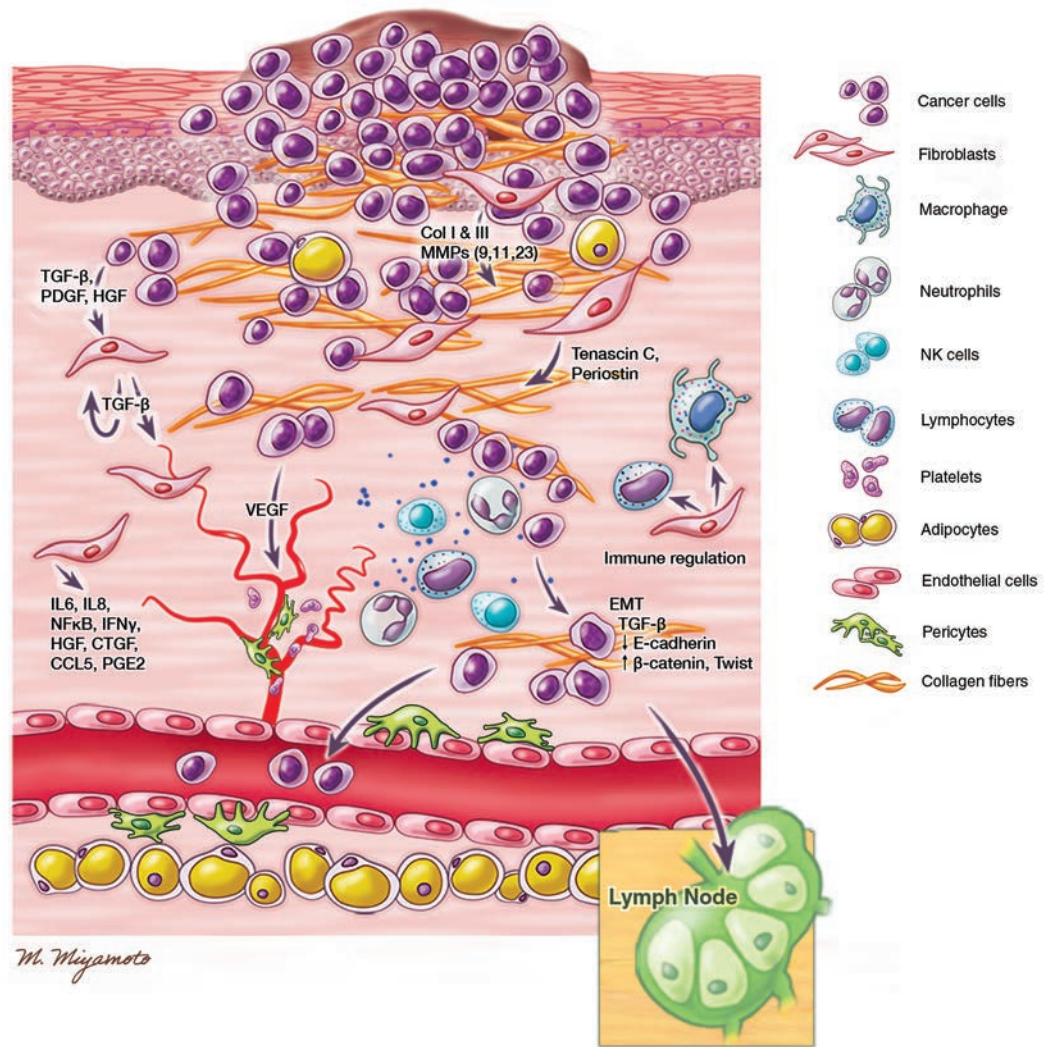
Figure 2. Detailed illustration of the tumor microenvironment showing representative cell types, tissues, and signaling factors involved. Fibroblasts are recruited by cancer cells and activated in the local environment via TGF-β, PDGF, HGF, and other signaling molecules. CAFs secrete TGF-β, which provides both a positive feedback mechanism encouraging fibroblast activation, as well as guiding the TME. CAFs also secrete paracrine signaling factors including IL-6, IL-8, NFκB, IFN-γ, HGF, CTGF, CCL5, and PGE2, as well ECM molecules such as collagens, MMPs, tenascin C, and periostin. Immune cells respond to the tumor, including neutrophils, lymphocytes, macrophages, and NK cells. Cytokines are secreted. Both cancer cells, via VEGF secretion, and CAFs are involved in stimulating angiogenesis. These new vessels are leaky and dysfunctional, which can limit immune access to the tumor. CAFs regulate the immune response. Cancer cells, under the influence of CAF signaling, can undergo EMT with downregulation of E-cadherin expression and upregulation of β-catenin and Twist, and escape through the basement membrane with access to vasculature for metastatic spread. Cancer cells can also collect in the lymph nodes and metastasize through the lymphatics. Illustrated by Mao Miyamoto.

are engaged in scar and keloid formation and also implicated in tumor stroma (32, 33) (Table 1). This heterogeneity is corroborated in humans, with some homology between species (16). Such surface marker heterogeneity makes this cell population challenging to study — no single cell surface marker is sufficient to capture a specific or unique cell population. Better understanding this heterogeneity and its functional significance is an area of active investigative research.

In the context of wound healing, dorsal dermal scarring in mice is attributable to the activity of fibroblasts derived from a lineage defined by embryonic expression of Engrailed-1 (*En1*) (33). *En1* fibroblasts also express FSP1, vimentin, Col1, and fibronectin. Notable exceptions in which scarless healing occurs include early gestational fetal skin (prior to E16.5) and the buccal mucosa (34, 35). Postnatally, *En1* positive fibroblasts (EPFs) stop expressing *En1* but are associated with expression of CD26/DPP4. Fibroblasts of the *En1* lineage contribute not only to scarring, but also to tumor stroma in mouse melanoma (33).

Table 1. Surface markers associated with activated fibroblasts in mice and humans

Markers	Significance in wound healing	Significance in tumor stroma	Reference(s)
α-SMA (α-smooth muscle actin, also known as acta2)	An intracellular protein expressed by fibroblasts transiently in mouse wound healing. Associated with increased fibroblast contractility. Also expressed by normal fibroblasts, smooth muscle cells, and pericytes. Upregulated in human scar tissue.	Upregulated in reticular (in mice), activated fibroblasts in both the tumor stroma and wound healing contexts in mice and humans. High CAF α-SMA expression is associated with poor prognosis in human breast cancer.	7–9, 27, 28, 149, 150
FAP (fibroblast activation protein, also known as F19)	Absent from adult tissue-resting fibroblasts but strongly induced during scar formation. Upregulated in activated fibroblasts.	F19+ fibroblasts found in primary and metastatic colorectal, breast, bladder, ovarian, and lung carcinomas. Intratumoral FAP expression correlates with poor prognosis in human colon cancer. CAF FAP expression related to checkpoint inhibitor resistance in mice.	39, 43, 144, 151
PDGFRα and -β (PDGFRα also known as CD140α)	PDGFs induce fibroblast reactivity and fibrosis. Expression associated with fibroblasts involved in organ fibrosis and wound healing in mice and humans. Expressed by dorsal, scar-forming fibroblasts in mice. PDGFRβ is also expressed by normal pericytes.	Involved in recruitment and phenotypic remodeling of CAFs. Found to be robustly expressed by CAFs in mouse squamous cell carcinoma.	19, 30, 33, 39
FSP1 (fibroblast specific protein-1, also known as S100A4)	FSP1 and α1β1 integrin expression are associated with a quiescent fibroblast phenotype in mice. FSP1+ fibroblasts are predominant cell types within experimental granulation tissue during wound healing at day 22 in a mouse model.	FSP1 expression found to identify a unique cohort of CAFs independently from cells expressing α-SMA and PDGFRα/b. FSP1+ CAFs facilitate malignant progression. In mouse melanoma, PDGF-CC paracrine signaling recruits CAFs expressing PDGFRα, α-SMA, and FSP1. Also expressed by some carcinoma cells. FSP1 deficiency in a mouse mammary carcinoma model yielded decreased tumor growth.	10, 11, 19, 31, 39, 152, 153
Vim (vimentin)	Expressed by quiescent and activated fibroblasts. Expression critical for fibroblast proliferation. In vim-deficient mouse wounds, fibroblasts do not proliferate, which inhibits TGF-β1 signaling and Slug, yielding dysfunctional wound healing. Also expressed by other mesenchymal cells.	Expression necessary for fibroblast initiation of EMT in tumor cells. Also expressed by epithelial cells that have undergone EMT.	36, 39, 154
Col-I and Col-III (collagen I is protein product of Col1A1 and 1A2, collagen III is protein product of COL3A1 gene)	Upregulated in fibroblasts involved in scar formation and fibrosis. Secreted by En1-expressing fibroblasts in mouse wound healing Major population of human fibroblasts expressing SFRP2/DPP4 associated with collagen bundles.	Upregulated in CAFs. Mesenchymal stem cells can differentiate into fibroblastic cells expressing α-SMA and Col-I in human lung tissue.	33, 137, 155
EGF	Expressed by wound healing fibroblasts; aberrant levels promote pathologic tissue fibrosis.	Activates EMT in cancer cells. Induces heparin-binding EGF overexpression in CAFs, fostering tumor progression.	137
ED-A (fibronectin spiced variant)	A mesenchymal marker, upregulated in activated fibroblasts.	Expressed by CAFs, as well as carcinoma cells and tumor blood vessels. Increased urinary ED-A associated with poor prognosis in human bladder cancer.	137, 156, 157
Postn (periostin)	A tissue repair product; levels in wounds correlate with activated fibroblast presence in granulation tissue.	Expressed by CAFs in colon cancer. Upregulated in human pancreatic stellate (fibroblastic) cells; deposition seen at carcinoma cell infiltration sites.	38, 158, 159
Desmin	Expressed by fibroblasts in hypertrophic stars and fibrosis in humans.	Also expressed by perivascular cells.	160
Podoplanin	Displayed by human dermal fibroblasts in sclerosis (along with CD 90).	Marks a specific CAF population. Prognostically relevant in lung, breast, and SCC. Also expressed by lymphatic endothelial cells.	161, 162, 163
FGF2	Involved in fibroblast activation in both acute and chronic tissue injury.	Binds tyrosine kinase receptor and induces VEGF expression.	39, 164
CD26 (also known as dipeptidyl peptidase-4 [DPP4])	Associated with mouse papillary fibroblasts population. Expressed by En1+ fibroblast in the mouse dermis. Expressed by human dermal SFRP2+ fibroblasts.	Fibroblasts of En1 lineage (expressing CD26/DPP4) contribute to tumor stroma in mouse melanoma. When these fibroblasts are ablated (via diphtheria toxin), tumor burden decreases.	33, 165, 166
CD90 (also know as thymocyte antigen 1 [Thy1])	Expressed by human dermal fibroblasts. Displayed by dermal fibroblasts in sclerosis (along with Podoplanin) in humans.	High CD90-expressing CAFs promote tumors more than low CD90-expressing CAFs in human gastric and prostate cancer.	161, 167
NG2 (neuron glial antigen-2)	Expressed by migratory fibroblasts in response to injury in vitro.	Expressed on normal and intratumoral pericytes. Pericytes distinguished by regulator of G-protein signaling 5 (RGS5) expression, which associates with CD31 rather than α-SMA.	168, 169
Tenascin-C	Involved in recruiting fibroblasts to wounds.	CAF expression involved in regulating carcinoma cell adhesion.	37, 170

In humans, a major population of fibroblasts expressing SFRP2/DPP4 is associated with collagen bundles, likening this population to the scar-forming *En1* population in mice (33). This population was not found to stratify specifically to the papillary or reticular regions in the skin. Other markers associated with activated fibroblasts in mice and humans include α-SMA, vimentin (36), PDGFRβ, fibroblast-associated protein (FAP), neuron glial antigen-2 (N2G), tenacin-C (37), desmin, periostin (38), THY1 (CD90), and podoplanin (24, 31, 39) (Table 1).

Striking lineage plasticity is observed in activated fibroblasts in the setting of both healing wounds and tumor proliferation (2). For example, in wound healing, myofibroblasts are capable of differentiating into adipose cells, through BMP signaling (40). Such lineage flexibility highlights the importance of considering cellular activities in a context-dependent fashion. In tumors, heterogeneity also exists between the number and proportion of CAFs between different cancer types (6, 41). For example, breast, pancreatic, and lung cancers have relatively high numbers of fibroblasts, while other tumors such as brain and ovarian contain few fibroblasts (24).

One reason driving the investigative interest in understanding and classifying CAF surface marker expression is that the patterns and relative levels of marker expression may be prognostic. For example, in a breast cancer study, higher FSP1 expression correlated with shorter overall survival (42). Similarly, a colon cancer study showed that high intratumoral FAP expression correlates with worse prognosis (43). However, complicating this finding, it is important to note that FAP expression is not limited to CAFs and has also been detected in epithelial cancer cells (24). These functional differences are key in determining the clinical significance of such observations.

CAFs. The precise origin of fibroblasts in solid tumors remains unclear. Some studies suggest a heterogeneous origin, in which BM cells are recruited to transdifferentiate into fibroblasts (44); however, other findings implicate a local expansion of tissue-resident cells. Regardless of their origin, CAFs play a fundamental role in tumorigenesis. When human mammary epithelial cells were transformed and implanted into nude mice, fibroblast coinjection yielded more efficient tumorigenesis (45). In a model of squamous skin carcinogenesis, ultrasound studies showed that coinoculation of tumor cells with CAFs yielded less necrotic and more vascularized tumors than when cancer cells were administered alone (30).

CAFs can direct specific cancer cell activities. For example, CAFs induce angiogenesis and tumor growth in association with expression of stromal cell-derived factor 1 (SFD1), also known as CXCL-12 (46). CAFs also express transcription factors such as SNAIL1, which drive EMT in cancer cells leading to invasion and metastasis (47). Just as CAF surface markers can differ based on cancer type, so too can their roles within a tumor. CAFs express a specific proinflammatory gene signature in pancreatic and breast cancer (30). Proinflammatory CAFs recruit macrophages (30), which in turn are proangiogenic in mouse skin and cervical cancer models secondary to MMP-9 secretion and VEGF stimulation (48).

Once activated in tumors, CAFs secrete a wide variety of cytokines that regulate other stroma cell activities. These include IL-6, involved in modulating inflammation, cancer progression, and tumor angiogenesis (24, 39), IL-8, IFN-γ, HGF, CTGF, CCL5, prostaglandin E2 (PGE2) (39) and NFκB, which promote inflammatory pathways that enhance tumorigenesis (30) (Figure 2 and Table 2). IL-6 is also fundamentally important in cutaneous wound healing (49).

Several papers have suggested that the tumor suppressor p53 can be mutated or epigenetically inactivated in CAFs (50–53). In vitro, coculture experiments using p53-deficient fibroblasts yielded greater cancer cell proliferation than coculture with WT fibroblasts, suggesting that stromal p53 expression exerts a detrimental effect on tumor growth (54). In vivo studies in p53-KO mice showed that α-SMA and tetraspanin (12) expression was notably increased, which correlated with increased cancer cell proliferation (55). In breast cancer, stromal cell p53 mutations were associated with poor prognosis and a higher incidence of nodal metastasis (51). On the other hand, robust p53 expression in stromal cells has been shown to potentially suppress tumor growth by generating an anti-TME, which occurs via macrophage function regulation (56).

Paradoxical role of fibroblasts in tumor stroma. While CAFs are known to support tumor progression, they also have poorly understood tumor-inhibiting effects (57). Tumors such as pancreatic ductal adenocarcinoma (PDAC) are characterized by extensive tumor and peritumoral fibrosis, known as desmoplasia. While desmoplasia is believed to be one of the reasons that cytotoxic therapies have limited effect in this cancer, when α-SMA–expressing activated fibroblasts were depleted in mice with PDAC, tumor growth increased and animal survival decreased (58). Similarly, in human PDAC, patients with fewer myofibroblasts in their tumors have decreased survival (58). This is thought to occur because depletion of fibroblasts may worsen tumor immunosuppression. Conversely, patients with robust desmoplasia have improved survival not only in PDAC, but also in lung and breast cancers (59). CAFs may induce tumor cell sensitization to therapy rather than resistance (60).

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Table 2. Cancer associated fibroblast cytokines, chemokines, and signaling molecules

Cytokines, chemokines, and signaling molecules	Significance in tumor stroma
TGF-β	Involved in fibroblast activation and deposition of abnormal ECM in wounds and tumors (62). CAF secretion of TGF-β induces EMT in breast carcinoma cells in humans (171) and promotes colorectal cancer progression and metastasis and correlates with poor prognosis (172). CAFs derived from mesenchymal stem cells (MSC) are recruited to gastric tumors by TGF-β, as well as SDF1α (173). When TGF-β II receptor was knocked out in mouse fibroblasts, the animals developed prostate neoplasia and stomach squamous cell carcinoma, which both showed increased numbers of tumor stroma cells. This is thought to occur secondary to paracrine HGF signaling. As such, CAF TGF-β signaling is both an activator and a modulator of tumorigenesis (63).
HGF (hepatocyte growth factor, also known as scatter factor [SF])	Fibroblast-derived HGF expression is associated with cancer initiation. HGF secreted by CAFs regulates tumor proliferation in various tumor types in mice and human cells (174). HGF secretion is associated with CAF-mediated tyrosine kinase (175) and epidermal growth factor receptor inhibitor resistance (176).
PDGF (composed of dimeric subunits, either PDGF-AA, -AB, -BB, -CC, or -DD)	PDGF-CC activates CAFs via paracrine signaling and drives tumor growth in mouse melanoma. The ECM protein osteopontin is a primary effector in this pathway (19).
VEGF (also known as vascular permeability factor, VPF)	Osteopontin, secreted by CAFs, stimulates endothelial cell VEGF-A signaling (19). In VEGF-A–KO mice, CAFs that secrete VEGF are recruited in a manner that is dependent on PDGFRα expression (177).
IGF1 (encoded by the IGF1 gene in humans)	Fibroblast secretion of IGF1 targets the ICF1 receptor on keratinocytes and promotes a protective response to UVB exposure in human. In older skin, IGF1 secretion is attenuated, resulting in ineffective protection against UVB exposure and driving tumorigenesis (178).
IL-6 (encoded by the IL-6 gene in humans)	Secreted by CAFs and involved in modulating tumor inflammation. CAF IL-6 secretion drives EMT and promotes metastatic spread via JAK2/STAT3 pathway signaling in gastric cancer (179). CAFs derived from MSCs express IL-6, as well as Wnt5a and BMP4, and promote tumor proliferation in a mouse model of inflammation-induced gastric cancer (173).
IL-8 (encoded by the CXCL8 gene in humans)	Secreted by senescent CAFs from pancreas tumors in vitro and in a xenograft mouse model. These IL-8–upregulated CAFs promote invasion and metastatic spread (180). Also expressed by human breast tumor adipose-derived stem cells (ASCs) (181).
NFκB (nuclear factor κ-light-chain-enhancer of activated B cells)	Promotes inflammatory pathways that enhance tumorigenesis. In a mouse squamous cell carcinoma model, CAFs gene expression patterns promoted angiogenesis, recruitment of macrophages, and tumor proliferation in a manner dependent on NFκB signaling (30).
CXC10 (CXC motif chemokine 10, also known as IFN-γ–induced protein 10 [IP10], encoded by the CXCL10 gene in humans)	A prometastatic chemokine, expression is stimulated by HIF1 (Hypoxia inducible factor 1) (182).
SDF1 (stromal cell–derived factor-1, also known as CXC12, encoded by the CXCL12 gene in humans)	Associated with CAF induction of angiogenesis and tumor growth. CXC chemokine expression also known to be involved in orchestrating functions in regulation of the wound healing process (46).
IFN-γ	An immunomodulatory cytokine produced by CAFs (183).
CTGF (connective tissue growth factor, also known as Cystine-rich, Connective Tissue, Nephroblastoma protein-2 [CCN2])	Member of the CAF secretome, associated with cancer cell proliferation and invasion (39).
CCL2 (also known as monocyte chemoattractant protein-1 [MCP1] or small inducible cytokine A2, encoded by the CCL2 gene in humans)	Prostate cancer CAF secretion of CCL2 (and CXCL12), stimulated by CXCL8 paracrine signaling, is associated with prostate cancer cell proliferation in vitro (184). Also associated with cell proliferation in in vitro breast cancer studies. CCL2 is also expressed by macrophages in the TME.
CCL7 (also known as monocyte chemoattractant protein 3 (MCP3))	Secreted by CAFs, as well as cancer cells and macrophages. Known to enhance carcinoma cell EMT, tumor proliferation, and invasion in a variety of cancers including gastric cancer, and it's overexpression (along with CCL21) is associated with poor prognosis (185).
PGE2 (Prostaglandin E2)	In a study involving CAFs derived from human hepatocellular carcinoma specimens, CAF secretion of PGE2 (along with IDO) suppressed NK cell activation, resulting in tumor progression (186). In vitro and mouse model research shows that CAF production of PGE2, induced by direct contact with B16 melanoma cells, plays an important role in melanoma cell proliferation (187).

In mouse and human breast cancer, paracrine signaling causes CAF upregulation of Chi3L1 in both primary and metastatic tumors, which promotes tumor growth via signaling with both cancer and immune cells (61). When fibroblast Chi3L1 expression was knocked down in an orthotopic mouse model, fewer activated (α-SMA–expressing) fibroblasts were detected and tumor growth decreased with increased mouse survival (61), a seemingly opposite effect compared with the aforementioned PDAC model. Thus, in different studies and tumor models, CAFs have a paradoxical effect in that their presence and activity can both stimulate and inhibit cancer growth and spread.

TGF-β — which is secreted by cancer cells, CAFs, and inflammatory cells in the microenvironment — is suspected to play a role in conferring this paradoxical effect related to CAFs. TGF-β promotes fibroblast activation and aberrant ECM deposition (62); however, if TGF-β signaling is eliminated, for example using a TGF-β type II receptor–KO mouse, neoplasia of the stomach and prostate is initiated (63). As such, it would seem that TGF-β is not wholly responsible for the paradoxical role that tumor fibroblasts play. RhoA has been proposed as a key regulator in the fibroblast transition from tumor inhibition to tumor promotion. RhoA-KO causes decreased α-SMA expression, decreased fibroblast contractility, and increased tumor stiffness (64). SDF1 (CXCL12) of CAF origin is also known to be protumorigenic both by stimulating cancer cells directly via their CXCR4 receptor, as well as recruiting endothelial progenitors for tumor neoangiogenesis (65).

Which and in what circumstances CAFs are beneficial versus detrimental to tumors, and the phenotypic and signaling determinants of these seeming opposing roles, has yet to be fully elucidated. This is an active area of research inquiry. Continued discoveries on this topic are crucial toward developing therapies that effectively target tumor stroma with minimal would healing compromise.

Acellular stromal elements of tumors and wounds

In addition to the cells of the stroma, the protein and interstitial components of the ECM are increasingly recognized for their complex contribution to wound and tumor biology (3, 4, 66). Overall, the former perception of the ECM as an inert structural framework over which autonomous cells enact biologic activities has been replaced by the recognition that the ECM is a dynamic manipulator of both wound healing and tumor behavior (3, 4, 66).

ECM components in the stroma. Fibrin, formed by the breakdown of plasma fibrinogen and deposited into the ECM, is found early in matrix formation along with fibronectin and vitronectin (67). Fibroblasts recognize fibrin and then replace it with collagen during granulation tissue formation (68). With regard to tumor growth, Dvorak suggested a tumorigenic role of fibrin, proposing that it may aid tumorigenesis by providing scaffolding for malignant cells, shielding tumor cells from immune attack, and assisting with angiogenesis (69). Recent evidence shows that fibrin may have an even more active role in mediating malignant progression — fibrin-embedded lung tumor cells increase levels of fibronectin and activate integrins, leading to upregulation of Slug, an important mediator of EMT and metastases (70). The fibrin network also promotes angiogenesis in both tumor progression and wound healing.

Fibronectin also has a prominent role in stromal behavior. Fibronectin stretching leads to differential exposure of binding sites, which provides a wide spectrum of interactions with both cells and other stromal proteins (3, 71). In wound healing, in vitro studies have shown that fibronectin is required for collagen I deposition and maturation into fibrils (72). Fibronectin also regulates LOX, which is responsible for collagen covalent cross-linking (73). Additionally, fibronectin stimulates fibroblast expansion, migration, and contraction in a TGF-β–dependent manner (74–76). Similar to the wound healing processes, colon cancer CAFs promote cancer cell invasion in vitro in a process dependent on fibronectin fibrillogenesis and adhesion via αVβ3 integrins (77). Fibronectin is also implicated in tumor angiogenesis. Specifically, increased ECM stiffness induces alternative splicing to produce a splice variant containing extra domain-B (EDB) type III repeat, which favors tumor angiogenesis (78), again illustrating the complex relationship between mechanical properties of the matrix and cancer phenotypes.

Collagen is another ECM protein that significantly influences stroma biology. In wound healing, fibroblasts deposit collagen during the proliferative phase, which allows fibroblast adhesion and migration through the wound (3). Wound tissue becomes stiffer due to collagen deposition and cross-linking that effects fibroblast morphology and gene expression (79). TGF-β is an important inducer of collagen synthesis in the wound, along with stimulating angiogenesis (80). Similar to wound healing, collagen affects tumors by modulation of the mechanical properties of the tumor bed. Human and mouse in vivo studies show that increased stiffness due to collagen thickening and linear conformation drive tumor invasion, mediated by LOX, FAK, and inte-

grin clustering (81, 82). CAFs modulate the specific geometric profile of this collagen network via paracrine regulation of cross-linking, which affects tumor cell migration and invasiveness (83, 84). On the other hand, disrupting collagen cross-linking via LOX inhibition reduces tumor activity (82). LOX levels are clinically prognostic in head and neck cancer (85). Tumor compaction and LOX activation have also been linked to increased VEGF levels and angiogenesis in a glioblastoma mouse model (86). In vivo studies show that collagen signaling stabilizes expression of the EMT regulator SNAIL1 (87).

Integrins. Integrins are adhesion receptors that anchor cells to the ECM and transduce mechanical stimuli to effect outside-in and inside-out signaling mediated by FAK and Src tyrosine kinases (66, 88). Integrin expression profiles reflect the tensile state of wounds to promote closure. For example, αVβ3 integrin expression increases with higher wound tension and augments α-SMA expression and cytoplasmic stress in fibroblasts in vitro (89). In tumors, integrins are crucial for cancer cell adhesion and invasion. Altering the TME fibrin network in vitro by adding platelet rich plasma modifies the integrin composition of the tumor stroma, which promotes tumor cell attachment (90). Additionally, integrin clustering is induced by tumor stiffness and leads to focal adhesion development. The downstream effects of this pathway include activation of cellular myosin by growth factors, as well as increased tumor cell proliferation, migration, metastases, and invasion (82, 91). Integrins are fundamental to CAF assembly of fibronectin networks to facilitate tumor invasion, especially integrin αVβ3 (77), which has been implicated in EMT and metastasis via Slug activation in vivo (70, 92). The local mechanism of tumor cell invasion is characterized by integrin attachment at the leading edge; conversely, proteolytic degradation of ECM fibers occurs at the trailing edge in vitro (93). Integrins are established activators of latent TGF-β and present active TGF-β to its cognate receptors via cell-cell contact (94–96). Finally, in vitro studies show that, when coupled with specific 3-D conformation of the TME, integrin upregulation switches on transcriptional factors required for tumor angiogenesis (97).

Interstitial glycans and glycosylated proteins. Hyaluronan (HA) is synthesized as a large glycosaminoglycan of repeating disaccharide and also exists in smaller fragments with distinct functions. In wound healing, high molecular weight HA leads to increased collagen III and decreased inflammation, while HA fragments increase inflammation and collagen I deposition, as well as myofibroblast differentiation and proliferation. Large pericellular HA molecules trap TGF-β next to fibroblasts, resulting in a positive feedback loop to maintain the myofibroblast phenotype (98). Conversely, HA fragmentation appears to support tumor growth by increasing blood vessel recruitment (99), as well as metastasis via the transcription factor TWIST in human breast cancer cells (100). Clinically, high levels of HA expression convey a poor prognosis in breast cancer (101).

Decorin is a proteoglycan recognized for it's important role in regulating fibroblast signaling (102). Decorin is a high-affinity TGF-β inhibitor (103) that substantially modulates stromal biology and has also been shown to regulate collagen fibrillogenesis and contraction (104, 105). Mouse decorin-KO models show delayed wound healing and increased fibroblast proliferation (106, 107). Like HA, decorin has a binary role in malignant spread: it is upregulated in quiescent, less aggressive forms of colon cancer (108), but KO can lead to intestinal tumor formation (109). In breast cancer, decorin downregulates ErbB2 tyrosine kinase signaling and blocks EGF, suppressing primary and metastatic progression (110, 111). However, high levels of decorin were also associated with lymph node disease and worsened survival with human proteomic profiling (112).

Protein-degrading ECM enzymes comprehensively modify stromal behavior in tumors and wounds, both by physical remodeling and regulation of proteins, cytokines, and proteases. Matrix metalloproteinases (MMPs), such as collagenase, gelatinase, and ADAMTS, modify the bioactivity of substrates, inducing changes in the interactions of these molecules with local cells and proteins (66). Early in wound healing, plasminogen is activated to plasmin to regulate fibrin degradation and fibrin matrix turnover, which influences downstream cellular behavior and protein deposition (113). In wound healing, MMPs facilitate cell migration, wound remodeling, and control bacterial invasion (114). This activity must be balanced, however, as overactive proteases are found in chronic wounds (115, 116). With regards to tumor progression, increased MMP activity confers invasive features to primary tumors (93). Microarray studies on human breast cancer show that MMP-9 is associated with more invasive tumors (117). Beyond the primary site, MMPs promote metastatic niches in lung cancer, and patients with lung metastases exhibit high levels of MMP-9 as compared with patients without distant disease (118).

The effect of immune cells within the tumor

Immune cells are important components of the wound and TMEs, and immunotherapies, such as checkpoint inhibitors and adoptive T cell therapy, are actively being investigated. In wound healing, immune cells prevent infection while the skin barrier is breached. Additionally, immune cell signaling promotes wound closure by stimulating granulation and reepithelialization (119). The immune response to tumors has multiple and paradoxical roles, similar to fibroblasts and matrix proteins (120). It is an important defense mechanism against cancer growth (121); however, malignant transformation often occurs in chronically inflamed tissue that can support cancer growth (122, 123). Tumor cells can escape immune defenses by creating an immune-privileged site (121).

Several immune cell types present in the tumor stroma are specifically implicated in cancer progression. Tumor associated macrophages (TAMs) produce proangiogenic cytokines that support new vessel and tumor growth, recapitulating the proangiogenic actions of macrophages in the wound healing response (124). Both TAMs and cancer cells secrete IL-10, which suppresses killer T cell function and antitumor defenses (125, 126). In mouse mammary carcinoma studies, antibody blockade of a specific TAM scavenger receptor increased tumor immunogenicity, leading to decreased tumor progression and metastasis (127).

Cytotoxic and innate T cell responses are crucial in host efforts to halt tumor proliferation. Solid tumors are characterized by the presence or absence of a T cell infiltrate. Having a prominent intra-tumoral T cell infiltrate is associated with increased progression-free survival in gastric and colorectal cancer (128, 129). In the context of wound healing, ablation of cytotoxic T cells in mouse models changes the composition of the wound inflammatory infiltrate but does not impair wound closure, strength, and collagen deposition (130). Tregs and myleloid-derived suppressor cells may be triggered to act in protumorigenic manner by inhibiting protective killer T cell action (131). However, in wound healing, Tregs may promote wound healing by attenuating IFN-γ and proinflammatory macrophage proliferation (132).

Wounds that become tumors

When cell stress is continuous and unrelenting, normal regenerative pathways can be derailed, and at times chronic wounds can ultimately result in neoplasia. Marjolin's ulcer describes an aggressive, ulcerating squamous cell carcinoma (SCC) in the setting of chronic wounds. Based on RNA-seq data, epithelial cells adjacent to Marjolin's ulcers show impaired ECM turnover, which may facilitate fibrosis and dysregulation of cell-cell adhesions related to EMT-associated cadherin signaling (133). Similarly, SCCs can form after tissue injury, such as actinic damage. Basal cell carcinoma (BCC) can arise from hair follicle cells secondary to the accumulation of mutations in follicular stem cells (2, 134). In a mouse skin biopsy model, BCC-like tumors formed 10 weeks after injury, suggesting that BCC may be triggered by injury and subsequent migration of follicular stem cells. Various other types of tissue injury, from surgical incisions to stomach ulcers, are linked to cancer (135, 136).

Tumor stroma and metastatic spread

CAFs are involved in tumor progression through a variety of mechanisms, including paracrine signaling in the TME and ECM deposition (137). However, the extent to which CAFs actually pave the way for metastases is still unknown. Interestingly, CAFs express proteolytic enzymes that are involved in collagen IV degradation (137, 138). Collagen IV is a primary component of the basement membrane, degradation of which is a critical component for tumor invasion.

Less than 1% of the cancer cells that escape into circulation from a primary tumor site are actually able to establish themselves as metastatic tumors (139). Microenvironmental factors both at the primary tumor and metastatic sites are likely critical determinants of metastatic success. Tumor-derived cytokines are important in mobilizing supportive cells at distant sites (139). Some studies suggest that activation of local fibroblasts to form new, tissue-specific CAFs develop in the setting of metastasis. Duda et al. found that, in some circumstances, cancer cells might bring CAFs with them from the primary site, including into the brain in human disease (140). If cell surface marker expression is maintained in CAFs that travel from a primary to a metastatic site, then therapies targeting primary tumor stroma might be similarly effective in the setting of distant metastatic disease.

Table 3. Clinical and preclinical stroma-targeting treatments

Therapeutic targets	Role in tumor stroma
PPARγ agonists	PPARγ is a transcription factor that inhibits fibroblast proliferation in wound healing (137). May also limit myofibroblast differentiation. Pioglitazone is a commercially available PPARγ agonist being explored for prevention and treatment of gastrointestinal mucosal damage after radiation (188, 189) and for fibrosis prevention in nonalcoholic fatty liver disease (NAFLD) (190). Suggested that Pioglitazone or other PPARγ agonists could have a role as an antistroma therapy.
Calcipotriol	The vitamin D receptor is expressed on human pancreatic tumor stroma. When treated with calcipotriol in preclinical studies, tumor stroma inflammation and fibrosis was decreased and pancreatic stellate fibroblasts reprogrammed back into a quiescent state (191).
IFN-β–expressing MSCs (mesenchymal stem cells)	In an ovarian cancer mouse model, i.p. injection of IFN-β–expressing MSCs (which differentiated into α-SMA–expressing myofibroblasts with activation), became incorporated into tumors and killed cancer cells via IFN-β–mediated caspase-dependent apoptosis (192).
Receptor tyrosine kinase inhibitors (e.g., Imatinib)	Imatinib is clinically used in the treatment of systemic fibrosis (143). Imatinib binds to the ATP-binding pocket of c-Abl, a downstream signaling molecule in the TGF-β pathway, and also blocks the tyrosine kinase activity of PDGF receptors. In a cervical cancer model, PDGF signaling blockade with Imatinib limited tumor growth.
AMD3100 (inhibits CAF CXCL12 production)	In an endogenous mouse model of pancreatic ductal adenocarcinoma, when FAP-expressing CAF production of CXCL12 production was inhibited with administration of AMD3100, T cells could access the cancer cells and checkpoint inhibitor therapy (αCTLA4 and αPDL1) became effective (144).
Anti–TGF-β antibodies (to improve αPDL1 therapy)	Administration of anti–TGF-β antibodies improved response to αPDL1 therapy by inhibiting CAF TGF-β signaling–mediated resistance to immunotherapy in a study on bladder cancer (145).
Protease inhibitors	Melanoma (147).
Anti-integrins	Melanoma (147).
Antibodies to CAF cell surface markers (e.g., FAP-α and FSP1/S100A4 CAFs in invasive lobular carcinoma)	Using antibodies to block CAFs, such as by targeting cell surface markers associated with CAFs including FAP-α or FSP1/S100A4 CAFs in invasive lobular carcinoma (42).
Modulation of PDGF-CC paracrine signaling	Modulation of PDGF-CC paracrine signaling in melanoma (19).
BMP signaling modulation	Based on the finding that BMP signaling is involved in myofibroblast lineage plasticity, altering the CAF phenotype could dramatically alter the tumor microenvironment in a way that might limit cancer cell proliferation and/or improve chemo-/immunotherapy efficacy (40).
Hyaluronidase	Ongoing trials exploring the use of hyaluronidase in conjunction with standard chemotherapy in the setting of metastatic pancreatic cancer (146).

Stroma as a therapeutic target

CAFs regulate cancer cells and the tumor immune response, and as such, present an important therapeutic target in treating cancer (24). In contrast to cancer cells, the genetic stability of CAFs make them an excellent therapeutic target (141). Further, therapeutically weakening the stroma may promote better access of traditional chemotherapeutic or immunotherapeutic drugs to cancer cells. In PDAC, the prominence of stellate fibroblastic cells is thought to limit chemotherapy access to the tumor.

Existing medications hold potential for disrupting tumor stromal elements (Table 3). Imatinib, a tyrosine kinase inhibitor commonly used to treat leukemia, as well as gastrointestinal stromal tumors (GISTs), is being used for treatment of systemic fibrosis (142). Imatinib binds to the ATP-binding pocket of c-Abl, an important downstream signaling molecule of TGF-β. In c-Abl–null cells, TGF-β–dependent induction of ECM proteins is decreased. Imatinib also blocks the tyrosine kinase activity of PDGF receptors. In a gastric cancer model, PDGF signaling blockade with Imatinib limited tumor growth (143).

CAFs play an important role in regulating the response to immunotherapy. A mouse PDAC study showed that FAP-expressing CAFs inhibited T cell infiltration and the response to immune checkpoint inhibitors (αCTLA4 and αPDL1). When SDF1 (CXCL12) production was inhibited with AMD3100, T cells accessed the cancer cells and checkpoint inhibitor therapy became effective (144). In a recent study exploring αPDL1 therapy in bladder cancer, fibroblast TGF-β signaling was found to play a dramatic role in resistance to immunotherapy. Coadministration of αPDL1 and aTGF-β antibodies increased therapeutic efficacy (145). Other ongoing trials are exploring the use of hyaluronidase, which targets tumor fibrosis, in

conjunction with standard chemotherapy in metastatic PDAC (146). These studies highlight the potential importance of anti-CAF therapies to improve efficacy of current chemo- and immunotherapies.

In melanoma, several therapeutic strategies targeting the tumor stroma have been explored, including protease inhibitors, receptor tyrosine kinase inhibitors, and antiintegrins (147). Other avenues that hold potential for antistroma therapies include PDGF-CC paracrine signaling in melanoma (19), antibodies to FAP-α and FSP-1/S100A4 CAFs in invasive lobular carcinoma (42), and targets to stimulate BMP signaling. Therapies to stimulate fibroblast differentiation to adipose tissue may also modulate the TME to limit tumor proliferation and/or improve chemo-/immunotherapy response (40).

There are many potential difficulties or challenges associated with targeting the stroma. Because these cells resemble normal, nontransformed cells, finding specific targets that will not kill healthy fibroblasts systemically, and consequently have significant implications for wound healing, is difficult. One way around this could be to approach stromal therapies from the goal of "reeducating" stromal fibroblasts rather than ablating them (148). Candidate agents have yet to be broadly identified (39). This path will likely receive significantly more exploration in the coming years as our knowledge of tumor stroma, and parallels with wound healing pathways, continues to expand.

Conclusion

Activated fibroblasts in wound healing and CAFs share many of the same pathways but with distinct characteristics. These fibroblasts and their associated distinct and complex ECM have a primary role in tissue repair and tumor proliferation. In tumors, controlling CAFs proliferation and activities may limit tumor progression and improve response to therapies. However, a more complete understanding of the paradoxical role of fibroblasts in tumors is needed to fully harness this opportunity. As we learn more about the subtleties of the dynamic actions of the stroma, we expect that therapies will continue to be developed that modulate stroma in both wound healing and tumors. If a tumor cannot grow without establishing a microenvironment, then cancer proliferation and metastases cannot occur. With more investigators exploring the important cellular, molecular, and immunologic factors within the tumor stroma, and harnessing the vast knowledge regarding wound healing that shares clear corollaries in terms of the microenvironment, the probability of future novel and exciting antistroma therapies will increase.

Author contributions

DSF, REJ, and RCR reviewed the literature and prepared the manuscript. MTL and JAN oversaw the literature review and guided preparation and review of the manuscript. All authors reviewed and approved of the final manuscript.

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