Cancer develops within a complex microenvironment critical to supporting tumor survival, growth, and metastasis. This tumor microenvironment (TME) is composed of a web of vasculature, extracellular matrix (ECM), stromal cells, immune cells, and soluble signaling molecules which form a dynamic “organ” critical to the pathophysiology of cancer. Within the TME, cancer-associated fibrosis has emerged as a critical regulator of cancer behavior. Indeed, fibrosis is a hallmark of cancer. Up to 20% of cancers are linked to chronic inflammation-related fibrosis (either from infectious or autoimmune etiologies) including hepatocellular, gastric, esophageal, head and neck, colon, pancreatic, cervix, and vulvar cancers. The impact of fibrosis on cancer initiation, progression, metastasis, and treatment outcomes have been increasingly studied however seemingly contradictory results leave the question unanswered: is fibrosis in cancer helpful or harmful? Perhaps fibrosis can be both helpful and harmful depending on the disease context. In this review, we will summarize our current understanding of the factors which drive tumor related fibrosis and how this fibrosis impacts cancer biology addressing evidence supporting fibrosis as a tumor restraining and tumor promoting factor and presenting a paradigm of a dual function of fibrosis in cancer.
CELLULAR SOURCES OF FIBROSIS

Fibrosis is the formation of excess connective tissue causing stromal hardening and scar formation. Desmoplasia is another commonly used term which refers to the growth of benign fibrous tissue secondary to tissue injury such as cancer or infection. Below we introduce the main cellular mediators of fibrosis and desmoplasia: fibroblasts, mesenchymal stem cells, fibrocytes, and stellate cells.

**Fibroblasts:** Fibroblasts are connective-tissue cells of mesenchymal origin. They are stromal cells which control tissue integrity. Fibroblasts maintain ECM homeostasis through both deposition of ECM and secretion of matrix metalloproteinases (MMPs) to remodel the ECM. Fibroblasts also regulate adjacent epithelial cells directing epithelial proliferation and differentiation. Further, fibroblasts moderate inflammation and aid in wound healing. While alpha smooth muscle actin (αSMA), fibroblast activation protein (FAP), S100A4, vimentin, and platelet-derived growth factor receptor-alpha are all expressed in fibroblasts, no 1 set of markers fully define these cells. This presents a challenge to delineate fibroblasts from other stromal cells and leads to significant heterogeneity within cells classified as “fibroblasts.” Fibroblasts are considered the main effectors of fibrosis in both normal and pathologic settings. During inflammation, fibroblasts become “activated” and are referred to as myofibroblasts which are the main collagen producers in the body. Fibroblasts associated with normal wound healing are phenotypically distinct from fibroblasts associated with cancer; fibroblasts within the TME are referred to as cancer-associated fibroblasts (CAFs) and they have a unique expression profile and function which significantly contributes to cancer-related fibrosis. In contrast to normal fibroblasts, CAFs have increased autocrine signaling ability and proliferation tendencies. CAFs are the major producer of ECM proteins within the TME thus drastically altering the physical properties of tumor stroma. The specific impact of CAFs on cancer biology will be discussed below.

**Fibrocytes:** Fibrocytes are hematopoietic stem cell-derived fibroblast precursors implicated in chronic inflammation, fibrosis, and wound healing. Fibrocytes are monocyte-derived cells with features of both macrophages and fibroblasts expressing CD34, CD45, CD11b, αSMA, and collagen I. Normal or classic fibrocytes serve as antigen presenters, augment immune reactivity, and mediate angiogenesis. In cancer, fibrocytes suppress the antitumor immune response acting as myeloid-derived suppressor cells. Within the TME, fibrocytes secrete ECM components and acquire a contractile phenotype similar to that of CAFs and fibrocytes have been postulated as a hematopoietic source of CAFs thus they are a mediator of tumor-associated fibrosis.

**Mesenchymal stem cells (MSCs):** MSCs are non-hematopoietic, multipotent stromal cells capable of differentiating into stromal tissues including fibroblasts, adipocytes, osteocytes, and chondrocytes. MSCs are an important source of fibroblast generation within the TME. MSCs are known for their role in wound healing and as MSCs are found in virtually all tissues from the bone marrow to the eyelid, they may serve as “first responders” to tissue injury. MSCs are also recruited to tissue in response to injury where they both modulate the immune response to dampen inflammation and aid in tissue repair through differentiation. Similar to fibroblasts, the characterization of MSCs is challenging given the lack of 1 identifying cell surface marker however, the International Society for Cellular Therapy established minimal criteria for defining MSCs: (1) plastic adherent in standard culture conditions; (2) express CD105, CD73, CD90 and lack expression of CD45, CD34, CD14, CD79a, and HLA-DR 3) and must differentiate into at least 2 of the following: osteoblasts, adipocytes, and chondrocytes.

As tissue resident cells, MSCs are present within the TME of most cancers. As with fibroblasts, normal tissue MSCs are phenotypically distinct from MSCs found within the TME. MSCs within the TME are referred to as cancer educated or cancer-associated MSCs (CA-MSCs). CA-MSCs uniquely impact the TME compared to normal tissue-derived MSCs and are critical players in tumor-associated fibrosis.

**Stellate cells:** Stellate cells have many similarities to MSCs. They are so closely related that they have been postulated to be a subtype of tissue specific MSCs. Stellate cells reside within the perisinusoidal space between hepatocytes and sinusoidal endothelial cells within the liver and the exocrine regions of the pancreas. At rest, stellate cells serve as reservoirs of vitamin A. Hepatic stellate cells have progenitor cell characteristics with the capacity to differentiate into fibroblasts, endothelial cells, and hepatocytes. While no lineage tracing studies have been performed, stellate cells are thought to be the primary source of fibroblasts within the liver and possibly the pancreas thus they are likely to be important players in liver and pancreatic cancer related fibrosis.

ROLE OF FIBROSIS IN CANCER INITIATION

Chronic inflammation results in fibrosis. As cancer is a disease of chronic inflammation mimicking a “non-healing wound,” similar mechanisms likely drive fibrosis in cancer. Indeed, chronic fibrosis predisposes to
This has been reviewed elsewhere in detail. Briefly, after tissue injury, wound healing occurs through a step-wise process of coagulation, inflammation, cell proliferation, inflammatory suppression, angiogenesis, and finally tissue remodeling. In the setting of ongoing inflammatory stimulus, this cycle can either stall or be continuously activated leading to a chronic, non-healing wound. As a result, rather than normal, healthy remodeled tissue, a fibrotic phenotype emerges. This fibrosis can then directly impact epithelial cell differentiation, epithelial mesenchymal transition, and epithelial proliferation. Cancer mimics this process due to dysregulated cancer cell proliferation inducing chronic proinflammatory stimuli, altered immune infiltration, leaky vasculature, and hypoxia ultimately creating a fibrotic TME.

TREATMENT-RELATED DRIVERS OF CANCER FIBROSIS

In addition to cancer-induced chronic inflammation as a driver of fibrosis, cancer treatments also play an important role in creating the fibrotic TME. Organ fibrosis, most notably pulmonary fibrosis, is a known toxicity of multiple chemotherapeutic agents including bleomycin, gemcitabine, and methotrexate. In vitro and in vivo studies demonstrate chemotherapy may promote an inflammatory and fibrotic microenvironment likely through tissue injury related to oxidative stress. Tissues exposed to chemotherapy undergo similar stages of wound healing including inflammation with influx of immune cells, followed by fibroblast activation and proliferation and remodeling which involves the accumulation and cross-linking of ECM. The development of fibrosis in tissues treated with chemotherapy is widely reported in cancers including colorectal, prostate, breast, cervix, esophageal, ovarian, and head and neck cancer. Chemotherapy-induced fibrosis may also be prognostic. For example, after neoadjuvant chemotherapy in rectal cancer, malignant cells are replaced by a fibroinflammatory milieu and increased fibrosis is correlated with worse outcomes. Radiation therapy is also a known driver of fibrosis. Radiation generates hypoxia and results in immune system activation which drives a CAF phenotype. This results in cellular damage and concludes with tissue inflammation and fibrosis generated by irradiated fibroblasts. These irradiated fibroblasts secrete MMPs which cause cystic, disorganized growth of new epithelial cells. Interestingly, desmoplastic unirradiated tissue is also thought to be inherently radio-resistant. Likely related to both the impact on the cancer cell and the fibrotic response, disease that recurs within a previously irradiated field is extremely therapy resistant. Thus, mainstays of cancer treatment may also enhance the development of tumor-associated fibrosis.

IMPACT OF FIBROSIS ON CANCER BIOLOGY: DUALITY OF FUNCTION

While long recognized as a key feature of the TME, the impact of fibrosis on cancer formation, growth, and progression is controversial. Below we summarize the literature supporting pro- and anti-tumorigenic roles of fibrosis in cancer initiation, growth, and metastasis with Fig 1 graphically summarizing this duality of function.

Fibrosis enhances cancer growth and progression. Fibrosis has been reported to support cancer growth through a variety of mechanisms including direct cellular interactions, immune modulation, and ECM remodeling. As a stromal progenitor cell, MSCs significantly impact the formation of the TME and are important mediators of fibrosis. After undergoing cancer stimulation or education, normal tissue MSCs are converted into CA-MSCs which subsequently enhance cancer cell proliferation, chemotherapy resistance, metastasis, and immune evasion. In ovarian cancer, CA-MSCs form a BMP4:HH positive feedback loop with cancer cells that enhances ovarian cancer growth, chemotherapy resistance, and enriches the cancer stem-like cell pool (CSCs). CA-MSCs also secrete IL6 and LIF which play redundant roles in supporting ovarian cancer proliferation and highlight the multilayered signaling between CA-MSCs and tumor cells.

In breast cancer, CA-MSCs communicate with cancer cells via exosomes to enhance the proliferation and metabolic activity of cancer cells. In pancreatic cancer, chemotherapy educated cancer cells and the fibrotic response, disease that recurs within a previously irradiated field is extremely therapy resistant. Thus, mainstays of cancer treatment may also enhance the development of tumor-associated fibrosis.

Fig 1. Dual roles of fibrosis in cancer. (A) Fibrosis acts to restrain cancer growth during cancer initiation however, after a process of cancer-mediated stromal reprogramming, (B) fibrosis acts to enhance cancer growth with stiffened ECM, enhanced angiogenesis, and suppressive immune response. Abbreviation: ECM, extracellular matrix. (Color version of figure is available online.)
CA-MSCs form a CXCL10: CXCR3 signaling loop with cancer cells to increase CSCs and enhance resistance to gemcitabine treatment. CA-MSCs increase breast cancer cell mobility, invasiveness, and dissemination via a CCL5:CCR5 signaling loop. In a prostate cancer model, tumor-derived CXCL16 induces the recruitment and differentiation of MSCs into CAFs which then secrete CXCL12, thus enhancing metastasis. CA-MSCs increase ovarian cancer cell adherence and spread onto mesothelial cells leading to peritoneal metastasis. Cancer cell: MSCs fusion events have also been reported and hybrid cells demonstrate enhanced metastatic capacity.

MSCs are known to limit autoimmunity and suppress the inflammatory response. MSCs are considered “immune privileged” or “immune evasive” and multiple reports demonstrate an important role for CA-MSCs in cancer cell-immune escape. CA-MSCs resident in tumors are known to secrete immunosuppressive factors including prostaglandin E2, indoleamine 2,3-dioxygenase (IDO), nitric oxide (NO), IL-4, IL-5, IL-6, and TGFb. CA-MSCs also secrete soluble program death ligand 1 and 2 which suppress CD4+ T cells and enhance Treg formation. In cervical cancer, CA-MSCs impair the antitumor response through the generation of extracellular adenosine which down-regulates the proliferation and activation of cytotoxic T lymphocytes in tumor islets. In melanoma, CA-MSCs aid in immune evasion via increase iNOS expression facilitating the murine engraftment of B16 melanoma tumors. In line with this, MSC produced NO suppresses T cell function in a model of graft-vs-host disease. CA-MSCs also induce Tregs in breast cancer models via TFG-b signaling and recruit CD11b+Ly6c+ monocytes, F4/80+ macrophages and CD11b+Ly6g+ neutrophils via secretion of CCR2 in a mouse lymphoma model. CA-MSCs also alter macrophage polarity enhancing M2 polarization and promoting angiogenesis in melanoma and ovarian cancer models. Taken together, there is a strong body of evidence supporting the protumorigenic, immunosuppressive role of CA-MSCs in cancer.

Stellate cells, which as noted above, are similar to MSCs and may represent tissue specific MSCs in the liver and pancreas, likewise have parallel protumorigenic functions. Stellate cells enhance progression of hepatocellular carcinoma by increasing cancer cell proliferation, angiogenesis, and immune suppression as well as ECM secretion. Stellate cells enhance immune suppression in pancreatic cancer via sequestration of CD8+T cells and MDSC differentiation in an IL-6/STAT3 dependent manner. It is important to note that potential heterogeneity amongst isolated stellate cells including the presence of differentiated fibroblasts was not addressed in these studies.

Fibrocytes have also been reported to support cancer. Fibrocytes enhance melanoma lung metastasis via recruitment of monocytes to the premetastatic niche. Fibrocytes also enhance the proportion of CSCs and increase resistance to antiangiogenic therapy in mesothelioma and lung cancer models.

MSCs, stellate cells, and fibrocytes are all important sources of fibroblasts. Considerable evidence implicates CAFs and CA-driven fibrosis in the promotion of cancer. Compared to normal tissue fibroblasts, CAFs have a unique secretome characterized by proinflammatory proteins, growth factors, angiogenic factors, and altered ECM. A CAF transcriptomic profile found in squamous cell, breast, and pancreatic cancer and characterized by CXCL2, IL6, IL-1b, CXCL5, and TGFb upregulation correlates with tumor growth, macrophage recruitment, and neovascularization. CAF secretion of growth factors including hepatocyte growth factor, fibroblast growth factor, and platelet-derived growth factor receptor-alpha enhance breast, ovarian, and lung cancer proliferation. CAFs also enhance angiogenesis and metastasis via Vascular endothelial growth factor (VEGF) secretion and alteration of ECM regulators including tenascin C, MMPs, Ras homolog member A (RhoA), Rho-associated protein kinase (ROCK), and myosin II leading to increased stromal stiffness and altered mechanotransductive pathways. For example, CAFs via caveolin1 expression induce Rho- and force-dependent contraction, matrix alignment, and microenvironment stiffening leading to enhanced tumor invasion and metastatic potential in melanoma and breast cancer. Similar findings have been reported across multiple cancer types including colon, prostate, pancreatic, ovarian, and gastric cancers.

CAFAs are also known to direct both the innate and adaptive immune systems. CAF secretion of TGFb and prostaglandin E2 decreases NK cell-produced interferon gamma and alters the NK cell phenotype. Through secretion of CXCL12 and CCL2, CAFs recruit and polarize macrophages to a M2 immunosuppressive phenotype in prostate cancer. In melanoma, colon, hepatocellular, breast, and lung cancer, CAFs enhance the recruitment of MDSCs and promote Treg cells within the TME via TGFb and IDO secretion. IDO is an important driver of immune tolerance by regulating NK cells, T regs, and MDSCs likely through starving the TME of tryptophan and increasing the tryptophan-derived metabolite kynurenine. CAF secretion of VEGF, beyond its role in promoting angiogenesis, is also immunomodulatory
inhibiting dendritic cell maturation, increasing MDSC cells and directly inducing T reg cell proliferation. In a mouse model of colon cancer, VEGF enhances PD-1 leading to CD8+ T cell exhaustion. Targeting VEGF reverses PD-1 expression enhancing the antitumor immune response. CAFs also promote cancer via metabolic mechanisms. Metabolic coupling of cancer cells and CAFs have been demonstrated in multiple cancer types including prostate, pancreatic, breast, ovarian, lung, and leukemias. Metabolically reprogrammed CAFs decrease isocitrate dehydrogenase 3a leading to decreases in α-ketoglutarate thus stabilizing HIF1α promoting glycolysis even under normoxic conditions. Aerobic glycolysis in CAFs provide lactate to cancer cells via the monocarboxylate transporter 4 thus supporting anabolic metabolism in cancer cells. This “lactate shuttle” is critical for cancer cell survival and growth. CAFs have also been reported to provide critical amino acids such as glutamine and lipids to tumor cells as further mechanisms to support cancer growth.

In addition to cellular contributions, ECM desmoplasia is also implicated in cancer progression. A densely desmoplastic TME promotes tumor growth by mechanically altering changes in blood flow resulting in notable tumor hypoxia, decreased drug delivery, and decreased immune infiltration, ultimately increasing resistance to chemotherapy, radiation, antiangiogenic, and immunotherapy. Also, the increased stiffness and change from wavy to linear collagen arrangement directs tumor cell intravasation and enhances metastasis. For example, in breast cancer, tumor cells migrate along linearized, stiff collagen fibers to facilitate metastasis. This has also been demonstrated in other cancers such as hepatocellular carcinoma.

Fibrosis is important in not only established tumor sites but also in the creation of a premetastatic niche. In vivo models demonstrate increased fibronectin expression in the stroma of future metastatic sites. This premetastatic change in stroma is associated with bone marrow-derived cell recruitment and primes future metastatic sites with increased angiogenesis prior to the establishment of metastatic disease. In a colon cancer model, tissue inhibitor of metalloproteinases (TIMP-1) increased the formation of a premetastatic niche within the liver where CAF-related factors such as SDF-1, fibronectin, TFGb, and S100A4 were all elevated. Interestingly, TIMP-1 is a reported activator of CAFs therefore implying that creation of the premetastatic niche may be dependent on CAF function. Lysyl oxidase, an enzyme responsible for collagen crosslinking associated with fibrosis and primary tumor growth, is also elevated at premetastatic sites prior to the arrival of disseminated tumor cells. Lysyl oxidase crosslinks collagen IV, drives the recruitment of CD11b+ myeloid cells, and bone marrow-derived cells, alters ECM patterns, increases angiogenesis, and facilitates malignant cell recruitment into the premetastatic niche.

FIBROSIS LIMITS CANCER GROWTH AND PROGRESSION

In contrast to the data discussed above, there is a body of evidence which argues that tumor-related fibrosis restrains cancer initiation, proliferation, and metastasis. In models utilizing normal stromal cells, both fibroblasts and MSCs have been reported to inhibit cancer growth. These results are complicated by the heterogenous source of normal stromal cells used (bone marrow vs resident tissue derived) which impacts the effect of stromal cells on tumor growth. Ganciclovir-induced ablation of αSMA-thymidine kinase (TK) expressing fibroblasts during the formation of premalignant pancreatic intraepithelial neoplasia (PanIN) lesions or early carcinoma stages lead to more aggressive tumors and decreased mouse survival. Interestingly, enhanced immune suppression was noted with increased CD4+Foxp3+ Tregs in the αSMA depleted tumors.

Investigations into a critical fibrosis signaling pathway, hedgehog (HH), also supports a restraining function of stromal cells in some cancers. Tumor cell-derived HH signals in a paracrine fashion to adjacent stroma to drive fibrosis. This has been well-documented in pancreatic, colon, and bladder cancer. Interestingly, epithelial HH deletion in a mouse model of pancreatic cancer initiation (Pdx1-Cre;Kras12‡; p5312‡;Rosa26LSL-YFP‡ (PKCY) model) decreases stromal content but results in more aggressive, poorly differentiated, and highly vascular tumors. Similarly, genetic and pharmacologic HH inhibition accelerates the development of premalignant PanIN lesions and promotes the progression of PanIN into invasive pancreatic cancer. Deletion of Shh in the murine pancreatic epithelium in KCS mice (Ptfla-Cre;Kras12‡;Shh012) enhanced the formation of PanIN lesions. Additionally, HH agonists induce stromal hyperplasia but decrease epithelial proliferation likewise suggesting stromal desmoplasia plays a restraining role in cancer initiation. Elegant mouse models with genetic disruption of tumor to stroma paracrine HH signaling via stromal knockout (KO) of the HH receptor, SMO, enhance the development of bladder cancer further supporting the importance of stromal HH signaling in restraining cancer growth. This is consistent with a critical role for HH signaling in normal epithelial...
differently, knockdown of 2 of the 3 known HH coreceptors (GAS1 and BOC) in fibroblasts enhances the ability of fibroblasts to support pancreatic cancer while KO of all 3 (GAS1, BOC, and CDON) prevents fibroblasts from supporting cancer growth.\textsuperscript{137} A pilot study of Vismodegib (a SMO inhibitor) with gemcitabine in pancreatic cancer demonstrated decreased fibrosis in paired pre- vs post-treatment biopsy specimens in 45% of evaluable patients but overall median fibrosis score was unchanged.\textsuperscript{138} In other cancers, pharmacologic inhibition of HH is associated with a stromal-dependent reversal of chemotherapy resistance.\textsuperscript{30,139–141} Collectively, this work highlights the complexity of stromal HH signaling and implicates a dose-specific role of HH in cancer promotion.\textsuperscript{137} As embryonic patterning is directed by HH gradients during development, a nuanced effect where varying levels of HH induce different phenotypes in cancer is perhaps not surprising.\textsuperscript{142,143}

**THERAPEUTIC TARGETING OF FIBROSIS IN CANCER**

Highlighting the importance of CAFs in cancer, genetic, pharmacologic, and immunologic targeting of specific subsets of CAFs dramatically impacts tumor growth. As mentioned above, there is not 1 specific marker to define fibroblasts but $\alpha$SMA, FAP, and S100A4, while likely marking phenotypically distinct subsets of fibroblasts (discussed further below), are often used to identify fibroblasts. A S100A4 knockout mouse demonstrates significant decreases in breast cancer initiation and metastasis which is restored with co-growth of tumor cells with S100A4 positive fibroblasts.\textsuperscript{144} Targeting FAP+ fibroblasts with an antibody conjugate inhibits tumor growth and leads to complete regression in xenografts of lung, pancreas, and head and neck cancer.\textsuperscript{145} Chimeric antigen receptor T cell therapy designed against FAP+ fibroblasts alone or in combination with CAR T cells against a tumor antigen leads to a significant survival advantage in a mouse lung cancer model\textsuperscript{146} and in other solid tumor models.\textsuperscript{147,148} Additionally, depletion of FAP via genetic KO or pharmacologic inhibition decreases lung and colon cancer growth.\textsuperscript{149} Selective depletion of FAP+ CAFs via expression of the human diphtheria toxin receptor in FAP+ cells followed by diphtheria toxin administration enhances antitumor immunity and induces synergistic effects with anti-PDL1 checkpoint therapy in pancreatic cancer.\textsuperscript{150} However, given the evidence discussed above of a dichotomous role of tumor-associated fibrosis both inhibiting and promoting cancer, caution needs to be taken when considering therapeutic approaches to target tumor stroma. Clinical trials using HH inhibitors have failed to demonstrate benefit in colon cancer.\textsuperscript{151} Further, while there are concerns related to the trial design and patient population chosen, a phase II trial in pancreatic cancer was halted early due to concern for inferior outcomes in the HH inhibitor arm.\textsuperscript{152–154} This may relate to the specific role of HH in the pancreas, the dose dependency of HH signaling or unanticipated effects of stromal depletion such as infiltration of immunoinhibitory cells as noted during stromal targeting in murine models of pancreatic cancer.\textsuperscript{133} Moving forward, it will be important to understand the tissue/tumor specificity of stromal effects and the impact of stromal targeting on all aspects of the TME when designing future clinical trials. Given the preponderance of data for fibrosis as a therapeutic target, despite the negative experience with HH inhibitors, we believe fibrosis and the desmoplastic stroma remains a potential therapeutic target for cancer.

**CONCLUSIONS, THE DUALITY OF FIBROSIS IN CANCER**

Clearly fibrosis and the cellular drivers of fibrosis are important in cancer biology but how are the seemingly discordant findings that fibrosis enhances and inhibits tumor growth to be reconciled? One potential reason for these differing conclusions may arise from generalizing results from studies focused on tumor initiation or early stage tumors and advanced metastatic cancer. Tumor-associated stroma in metastatic disease is likely significantly different than stroma found at the primary site or within premalignant lesions. Broadly concluding that fibrosis supports or inhibits cancer is an over simplification. In actuality, the effect of fibrosis is context-dependent and likely both inhibits and supports cancer under certain conditions. A recurring theme within cancer stromal research is the duality of function of most stromal cells. As described in both MSCs and fibroblasts, stromal cells within normal tissue behave differently than their tumor-educated counterparts. The tumor “educates” normal stromal cells converting them into cancer promoting cells. Fibroblasts become activated to a CAF phenotype.\textsuperscript{155} MSCs become reprogrammed into CA-MSCs\textsuperscript{55}. Evolutionarily, mesenchymal-derived stromal cells direct epithelial differentiation and are critical to maintaining appropriate tissue structure, hence their importance in wound healing. Indeed, the normal function of these stromal cells is to prevent pathologic states such as tumor growth. Thus, depending on the state of the stromal cells (normal vs cancer educated), divergent roles in tumor growth (suppression vs enhancement) are expected.

Additionally, the source of stromal cells likely dramatically alters their impact on cancer behavior. Each
cancer has its own pattern of metastasis indicating disease-specific tissue tropism. For example, while genetically similar cancers, triple negative breast cancer and high grade serous ovarian cancer have distinct metastatic patterns with breast cancer frequently metastasizing to the bone while ovarian cancer colonizes the abdomen and rarely metastasizes to bone. This may indicate a tissue-specific ability of cancer cells to convert normal stroma into cancer supporting stroma. We recently demonstrated ovarian cancer converts normal omental and ovary-derived MSCs into protumorigenic CA-MSCs but fails to convert bone marrow-derived MSCs (BM-MSCs) into ovarian cancer supporting CA-MSCs. In contrast, breast cancer cells functionally convert BM-MSCs into breast cancer supporting CA-MSCs. This work highlights the importance of tissue source in the formation of cancer promoting CA-MSCs. Further, reports of BM-MSCs enhancing prostate and breast cancer growth (cancers which frequently metastasize to bone) but inhibiting ovarian cancer growth (which rarely metastasizes to bone) is consistent with a tissue-specific capacity of stromal cells to support cancer growth. This may explain much of the divergent results depending on the tissue source of the stromal cells studied.

As SMA is regulated by the Rho GTPase signaling pathway, investigators noted the expected loss of αSMA expression in RhoA KO fibroblasts, however, there was no disruption of FAP expression. Indeed, the remaining FAP+ fibroblasts enhanced prostate cancer growth.

Building on these findings, another potential reason for the differing function of fibroblasts in cancer is the existence of subsets of fibroblasts which have divergent roles in cancer. Most notably, FAP and αSMA may delineate 2 such subsets. Fibroblasts with high FAP expression may be particularly important drivers of fibrosis and poor outcomes. In pancreatic cancer, FAP and fibroblast specific protein (FAP) high fibroblasts are associated with worse outcomes, while αSMA high fibroblasts are associated with improved outcomes. Targeting FAP+ cells using genetic KO, chimeric receptor T cells, and vaccine strategies inhibited tumor growth in lymphoma, melanoma, lung, pancreatic, breast, and colon cancer models. Thus, as noted above, FAP+ or FAP− stromal cells may differentially regulate tumorigenesis.

Finally, it is important to recognize the complex heterogeneity within the TME and that alterations in 1 compartment may have unintended effects in another. For example, targeting fibroblasts alone may remove a stromal barrier allowing immune infiltration but it is not clear if this immune infiltration will be pro- or antitumorigenic as cancers have multilayered approaches to hiding from the immune system. If the stromal barrier is removed but only immune-suppressive cells enter the TME, the overall outcome will be worse. However, if stromal targeting agents are combined with immune checkpoint inhibition, the net effect of removal of the stromal barrier may be beneficial. For example, in the αSMA-TK ganciclovir ablation mouse model of pancreatic cancer, the growth promotion effect of fibroblast depletion was reversed by using an
anti-CTLA4 inhibitor.\textsuperscript{133} It is possible that a similar approach combining stromal targeting with a HH inhibitor with immune modulation with an immune checkpoint inhibitor may demonstrate improved responses and that the lack of efficacy noted in the HH clinical trials may be due to targeting only half of the problem.

Overall, recognition of the TME as a vital contributor to cancer biology has yielded important insights on the importance as well as the complexity of fibrosis in tumor growth. The role of tumor-associated fibrosis is not one dimensional but dynamic, seeming to evolve during cancer progression and impacts multiple aspects of cancer biology. Targeting this fibrosis is an appealing approach to improving cancer outcomes. However detailed mechanistic studies are vital to understand the impact of such therapies within each specific disease context with emphasis on the stage of disease, subtype of fibroblasts affected, and compensatory changes within the TME which will drive cancer response.

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