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The fibrotic tumor stroma

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Introduction

Over the past two centuries, numerous clinical and pathological observations have established a clear relationship between chronic inflammation, fibrosis, and cancer (1). Skin fibrosis associated with recessive dystrophic epidermolysis bullosa leads to highly metastatic skin carcinomas (2). Progressive lung scarring associated with idiopathic pulmonary fibrosis is a risk factor for lung cancer development (3). Moreover, human pancreatic adenocarcinomas can be highly fibrotic, and experimental evidence in animals supports an etiologic role for fibrosis in pancreatic cancer progression (4, 5). Thus, fibrosis can precede or follow cancer development and may participate in multiple stages of tumorigenesis and metastasis. In this Review, we present recent findings on the composition of the fibrotic tumor stroma and how its mechanical and biochemical effects influence diverse intratumoral processes that determine the metastatic fate of tumor cells. We speculate on therapeutic opportunities, pose questions, and discuss future challenges in this rapidly expanding field.

Provisional matrix deposition in cancer: priming for fibrosis

The concept that tumors represent “wounds that do not heal” was put forward over 30 years ago (6). Subsequently, R.A. Clark coined the term “provisional matrix” to describe factors that appeared coincident with epidermal cell migration during skin wound healing (7, 8). In the context of fibrosis and cancer, the provisional matrix can provide initial instructions to resident and invading immune and inflammatory cells and stromal cell populations (i.e., perivascular cells, resident stem/progenitor cells, and quiescent fibroblasts) that activate them toward a pro-wound repair state (9) and, in certain cases, provide cues that stimulate epithelial-to-mesenchymal transition (EMT) and endothelial-to-mesenchymal transition (refs. 10, 11, and Figure 1). Although reparative during normal wound healing processes, the provisional matrix loses reparative capacity in the tumor stroma owing to physical and posttranslational modifications that occur during myofibroblast remodeling. Although deep proteomic sequencing of tumor matrices has revealed hundreds of proteins that are aberrantly expressed and/or modified (12), here we will address how several of the most abundant matrix components (fibrin, fibronectin, and collagen) can regulate mechanical properties of the tumor stroma.

The provisional matrix, composed primarily of fibrin and fibronectin, plays a critical role in angiogenesis, a process by which new blood vessels grow from existing vessels that is critical in healing wounds and is strongly associated with tumor progression. Rapid, disorganized angiogenic responses driven by tumor oxygen requirements result in persistent activation of the coagulation cascade and deposition of fibrin-rich early provisional matrix. In 2013, Iacoviello et al. found a strong correlation between plasminogen activator inhibitor-1 (PAI-1) and elevated risk of colorectal and breast cancer, suggesting that this critical regulator of fibrin persistence is a potential risk factor (13). Links between the coagulation cascade, fibrin persistence, and fibrosis are equally strong, suggesting a common pathway between cancer and fibrosis. For instance, mice overexpressing PAI-1 display enhanced fibrosis, whereas PAI-1 knockdown protects against fibrosis in various models, including bleomycin-induced lung fibrosis (14–16). In urokinase- and plasmin-deficient mice, fibrin persistence in injured muscle is linked to poor regeneration and replacement fibrosis (17, 18). While PAI-1 and other enzymes regulating fibrin degradation, such as urokinase, are perturbed in these mice, too are enzymes impacting the formation of fibrin. Procoagulant factors such as fibrinogen and factors VII and X are elevated in patients with intra-alveolar fibrosis (19). Thrombin, in particular, can directly stimulate fibroblast proliferation (20), extracellular matrix (ECM) production (21), and differentiation into myofibroblasts expressing α-smooth muscle actin (αSMA), all of which are characteristic of the tumor-associated fibrotic reaction known as desmoplasia (22). Fibrin persistence also greatly impacts the inflammatory milieu of the tumor stromal microenvironment because of fibrin’s ability to bind macrophage-1 antigen (Mac-1).
on classically activated macrophages. Fibrin engagement of Mac-1 leads to upregulation of the proinflammatory cytokines IL-1β, TNF-α, IL-6, and macrophage inhibitory protein-2 (MIP-2) (23). In models of dystrophic muscle (which present a strong fibrotic phenotype), persistent fibrin leads to increasing presence of alternatively activated macrophages (M2a) (21), which have been shown to promote fibrosis in several model systems (24, 25).

Fibronectin (FN), another key component of the provisional matrix, serves as a signal scaffolding and growth factor–depot protein through its multiple and spatially coordinated binding sites for receptors, growth factors, and other ECM proteins (26). Plasma FN is initially deposited into the interstitial space during fibrin polymerization, where it binds and is cross-linked to the fibrin-rich early provisional matrix. FN, like fibrin, can bind directly to invading inflammatory cells, vascular cells, and fibroblasts, where it triggers cell adhesion and invasion into the early provisional matrix. Invading fibroblasts secrete and assemble an elaborate FN-rich transitional ECM (the so-called late provisional matrix) that lays the foundation of tissue progression. FN-rich ECM generated by cancer-associated fibroblasts (CAFs) has been shown to be sufficient to drive desmoplastic differentiation of normal fibroblasts and can facilitate metastasis of cancer cells (27). FN can signal directly to cells through its ability to engage a wide range of cellular integrins (26), bind a plethora of growth factors (28), and spatially arrange growth factor receptors and integrins to facilitate synergistic signaling (29–31). Importantly, FN is a depot for TGF-β latent complex, where it has been shown to be physically coupled to the fibrillary FN matrix. This physical coupling ensures that TGF-β is readily available to cells despite transcriptional regulation of this key fibrosis-associated growth factor. The physical/structural nature of fibrillar FN matrix is also a key signaling characteris-
Fibroblasts arbitrate the desmoplastic reaction and cancer-associated fibrosis

If wound healing and fibrosis represent the progression of ECM deposition, degradation, and remodeling toward a more permanent collagen-rich ECM, then the fibroblast must be considered the arbiter of that progression. The host’s response to a growing tumor involves heterotypic interaction and paracrine signaling between cancer cells, vasculature, immune cells, and fibroblasts in the desmoplastic reaction within the tumor microenvironment (44–46). The fibroblasts within this reaction, which are collectively termed CAFs, have diverse origins and phenotypes (47). Studies on genetically engineered mouse models of cancer have revealed remarkable CAF heterogeneity (48). Several groups have attempted to define the heterogeneity of CAFs based on functional outcomes, which seems appropriate given the lack of definitive, fibroblast-specific markers. In one classification scheme, CAFs are clearly distinguished from quiescent, tissue-resident fibroblasts and even wound-associated activated fibroblasts. Tissue-resident fibroblasts are in a resting, nonproliferative, low metabolic state and, in some cases, are thought to serve as progenitor or stem cells (49). Wound-associated activated fibroblasts are characterized by loss of certain fibroblast markers (e.g., fibroblast-specific protein-1), acquisition of muscle-like markers (e.g., αSMA), increased ECM synthesis, and enhanced ECM remodeling (50–55). Key distinctions between the wound-associated activated fibroblast and CAFs or fibrosis-associated fibroblasts are the sensitivity of wound-associated activated fibroblasts to apoptosis and their ability to facilitate wound resolution through clearance by natural killer cells, a process known as nemosis, and/or dedifferentiation back to a resting state (52, 56). Furthermore, evidence suggests that CAFs, but not normal fibroblasts, support metastatic lesions (57), implying greater differences than simply a resistance to apoptosis. The exact mechanism driving this transition into a CAF or fibrotic fibroblast remains unknown but is likely an adaptive response to the chronic wound healing reaction and accompanying inflammatory milieu associated with the

![Collagen cross-linking in fibrosis and cancer](image-url)
emergent CAF subtypes that have opposing effects on clinical outcome, highlighting the importance of CAF stratification systems for future clinical efforts to target the tumor stroma. In a recent review, Kalluri proposed a more generalized classification of CAFs into tumor-restraining (F1), tumor-promoting (F2), secretory (F3), and ECM-remodeling (F4) (47). Whether such functional classifications appropriately stratify the diverse heterogeneity of CAFs and their broad impacts on ECM remodeling remains unclear.

**Fibrillar type I collagen and intermolecular cross-linking**

The tumor stroma transitions from a provisional matrix to a dense fibrosis by accumulating fibrillar collagens, among which type I collagen is the predominant component. Fibrillar collagen accumulation and stiffening can result from increased collagen synthesis that is driven by profibrotic cytokines, particularly TGF-β1, impaired collagen degradation due to an imbalance between matrix metalloproteinases (MMPs) and their inhibitors, and the formation of specific covalent intermolecular cross-links that render collagen fibers resistant to MMP-mediated degradation. The importance of TGF-β1, MMPs, and MMP inhibitors has been extensively reviewed elsewhere (63, 64). In the following section, we will review the basic collagen cross-linking chemistry and how it is altered in fibrosis and cancer.

Type I collagen, a heterotrimeric molecule composed of two α1 chains and one α2 chain, consists of three structural domains: amino-terminal nonhelical telopeptide, central triple-helical (helical), and carboxy-terminal nonhelical telopeptide domains (65). The central helical domain of each chain contains more than 300 repeats of X-Y-Gly sequence representing more than 95% of the polypeptide. In the collagen fibril, molecules are packed in parallel, longitudinally staggered with respect to one another by approximately 67 nm, and stabilized by covalent intermolecular cross-linking (Figure 2, A–C), which is the final step of collagen biosynthesis (for collagen biosynthesis, see refs. 66, 67). Cova lent intermolecular cross-linking occurs between telopeptide and helical domains on adjacent collagen molecules through interactions between key lysine (Lys), 5-hydroxylysine (Hyl), and histidine (His) residues (Figure 2, B and C). Cross-linking is a multistep process that is regulated at the levels of cross-link initiation, cross-link type determination, and cross-link maturation. At each level of regulation, Lys posttranslational modifications play critical roles and, with the exception of the final condensation reactions, are enzymatically controlled.

Helical and telopeptidyl Lys on collagen can be hydroxylated to form Hyl residues, and specific helical Hyls are further modified by O-linked glycosylation to produce galactosyl-Hyl (G-Hyl) or glucosyl-galactosyl-Hyl (GG-Hyl). Lys hydroxylation is catalyzed by lysyl hydroxylases 1–3 (LH1–LH3) encoded by procollagen-lysine, 2-oxyglutarate 5-dioxygenase genes (PLD1–PLD3) (68, 69), and, like prolyl hydroxylation, the reaction requires Fe²⁺, 2-oxoglutarate, O₂, and ascorbate (70). LH2 is the only LH family member that can hydroxylate Lys residues within the telopeptide sequences –X-Lys-Ala-, –X-Lys-Ser-, and X-Lys-Gly. LH1 hydroxylates primarily Lys residues within the helical domain of collagen (e.g., –X-Lys-Gly–), and LH3 functions principally as a glycosyltransferase by transferring a glucose unit...
to G-Hyl to form GG-Hyl (71, 72). The major glycosylation in type I collagen occurs at the helical cross-linking sites near the N-terminus, and it may regulate cross-link maturation (72–75). Recent studies showed that LHS are regulated by a number of ER-resident chaperones and foldases (76–82). Defects in these LH-associated proteins result in abnormal collagen cross-links that lead to bone and connective tissue disorders (81, 83, 84). These new findings clearly indicate that Lys modifications are tightly regulated at multiple levels and are critically important in connective tissue development.

Collagen cross-linking is initiated in the extracellular space by the action of lysyl oxidase (LOX) and LOX-like (LOXL) family members (for a review, see refs. 85–87), which catalyze the oxidative deamination of Lys and Hyl residues in the telopeptides, generating reactive aldehydes (Lysal and Hylal, respectively). These aldehydes then undergo a series of condensation reactions with vicinal Lysals, Lys, Hyl, and His residues to form tissue-specific covalent intra/intermolecular cross-links (ref. 65 and Figure 2, B and C). Lysals-derived collagen cross-links (LCCs), for instance, are particularly abundant in soft connective tissues such as skin and cornea (88–91). Hylal-derived collagen cross-links (HLCCs) are abundant in large load-bearing skeletal tissues such as bones and cartilage and are generally more stable than LCCs (89, 92). Cross-linking pattern is also altered under pathological conditions. For detailed chemistry and biology of collagen cross-linking, see several review articles (88, 92).

**How collagen cross-linking is altered in cancer**

LOX and LOXL2 levels are elevated in numerous cancer types (93–99). Secretion of LOX by tumor cells (96, 100) initiates collagen cross-linking and thereby stiffens tumor stroma, creating mechanical forces that trigger integrin-mediated formation of focal adhesions that initiate tumor cell invasion (101). Thus, LOX may drive metastasis, in part, by increasing the amount of collagen cross-links in tumor stroma. More recent studies have opened a new frontier of cancer research by showing that, in addition to the quantity of cross-links, the “type” of cross-links can also influence tissue mechanics within tumor stroma. This principle is based on several decades of research on fibrotic diseases. For example, in fibrotic diseases of the skin such as lipodermatosclerosis and keloid, the predominant types of cross-links switch from LCCs to HLCCs as a result of overhydroxylation of the telopeptide Lys residues (102, 103). Similarly, HLCCs are the predominant type of cross-link in fibrotic diseases of the lung (104, 105) and liver (106–108). The collagen cross-link switch in fibrosis results from increased expression of LH2 in fibroblasts (109, 110). In the initial studies on LH2 in cancer, several groups reported that high LH2 levels promote metastasis and are correlated with shorter durations of survival (111–116). Several of these studies showed that LH2 stabilizes and organizes the collagen matrix in tumor stroma. By comprehensively analyzing the collagen cross-links in cancer, we showed that LH2 increases HLCCs at the expense of LCCs, leading to a change in the predominant type, but not necessarily the quantity, of collagen cross-links (115). LH2 and LOX are coordinately upregulated in response to hypoxia and are direct targets of hypoxia-inducible factor-1α, suggesting that hypoxia regulates both the type and quantity of collagen cross-links as part of an integrated profibrotic response (112–122). The finding that cancer recapitulates the fibrosis-associated switch toward a high-HLCC, low-LCC state provides a potential biochemical basis for the prometastatic effect of LH2 (Figure 2C). Providing provocative evidence that the collagen maturation process can adversely impact clinical outcome, Keely and colleagues identified a paradigm of type I collagen maturation that is associated with tumor growth in genetically engineered mouse models of human breast cancer and applied those metrics to a human breast cancer cohort, which showed that the presence of type I collagen bundles that orient perpendicularly to the tumor boundary is correlated with a shorter duration of survival (123).

Until recently, LH2 was considered to be a dedicated resident of the ER, where it hydroxylates Lys residues on procollagen α chains before the formation of triple helix (66, 124). In that context, the finding that tumor cell–derived LH2 increases HLCC formation in tumor stroma is counterintuitive, because tumor cell–derived LH2 should have limited access to collagen originating from CAFs, the primary source of fibrillar collagen in tumor stroma (125). Two recent findings by our group offer a potential explanation to this apparent paradox. First, in addition to residing on the ER, LH2 is secreted by tumor cells and can modify collagen in the extracellular space (126). Second, LH2 is expressed not only in tumor cells but also in CAFs, which can switch the tumor stroma toward a high-HLCC, low-LCC state (61).

**Fibrosis and intratumoral immune surveillance**

Infiltration of innate and adaptive immune cells is a prominent feature of the activated tumor microenvironment. CAFs and tumor cells deposit matrix proteins and matrix-modifying enzymes that impact immune cell recruitment and function; conversely, activated immune cells modify the microenvironment in ways that affect matrix composition and structure, creating an interlocking cycle of immune cell recruitment and ECM production (Figure 3). The last few years have witnessed a revolution in cancer therapy based on immuno-oncology (127). A better understanding of the way in which cancer-associated fibrosis regulates immune cell function will be critical to developing improved immunotherapies.

In normal tissues, epithelial cells create an antiinflammatory milieu (128) and produce basement membrane structures that differentially regulate immune cell trafficking, activation, and function (129, 130). This model of tissue-based immune cell homeostasis depends on matrix composition, which includes fibrillar collagens (mainly type I, but also types II, III, V, and XI), nonfibrillar collagens, glycoproteins, and a mix of small and large proteoglycans (130, 131), to create architectural features that alter the ability of leukocytes to traverse the tissue by their use of non–integrin-dependent, non–protease-dependent mechanisms of migration (132, 133). As opposed to the more variable mesh-like architectures of interstitial and provisional matrix, basement membranes have a very dense protein network that functions to separate tissue compartments (134, 135). These structural and biochemical compositional differences are selective for immune cell migration. For example, immune cells adhere to the laminin 511 isoform, which is found in a patchy distribution on endothelial basement membranes and provides an inhibitory signal to cell migration, driving cells toward regions containing high laminin 411, an isoform that supports cell migration (130, 136, 137).
Intratumoral fibrosis and inflammation perpetuate each other through enzymatic and chemotactic mediators (138). For example, CAFs regulate the recruitment and activation of immune cells (139–142) through multiple mechanisms, including CXCL12 secretion (143, 144), establishment of a competitive metabolic microenvironment (145), and skewing of inflammation toward Th2 and Th17 responses (146–149). Proteolytic degradation of ECM components by MMPs and other enzymes exposes damage-associated molecular patterns (DAMPs) that trigger an orchestrated inflammatory response through pattern recognition receptors on immune cells (150, 151). This system is analogous to the DAMPs that initiate innate immune response to infection, the best characterized of which are the small leucine-rich proteoglycans decorin and biglycan that drive inflammation via activation of TLR2/4 signaling on macrophages, dendritic cells, and T cells. Beyond their biochemical actions, ECM molecules have architectural properties that govern immune cell function in tumors; for example, the spacing and orientation of collagen in tumors can have a “trapping” effect on T cells as described above for normal tissues (132, 133, 152–154). However, effector T cells and other immune cell types have been detected in areas of dense fibrosis in pancreatic cancer (155), arguing against a dominant role for mechanical impedance of immune cell infiltration by collagen. Conversely, immune cells that are recruited to early sites of neoplasia release cytokines that reprogram normal fibroblasts into CAFs (142) and MMPs that remodel collagen and activate the release of profibrotic cytokines (156). On the basis of evidence from wound repair models showing that the early fibrotic reaction driven by M1 macrophages and Th2 CD4+ T cells is eventually suppressed by a later influx of M2 macrophages and Th1/Th17 CD4+ T cells (156), intratumoral fibrosis is likely to be dynamic owing to maturation of intratumoral immunity during tumor progression.

Therapeutic implications

The fibrotic tumor stroma is an emerging target in cancer therapeutics. Antifibrosis drugs studied thus far in preclinical and clinical trials were recently reviewed (157). Two drugs recently approved for the treatment of idiopathic pulmonary fibrosis are of interest. Although its precise target is unclear, pirfenidone reduces tissue fibrosis, inhibits fibroblast proliferation, decreases the expression of profibrotic mediators such as TGF-β, reduces collagen synthesis (158–160), and suppresses the proinflammatory mediators IL-1β and TNF-α (161). Pirfenidone has demonstrated efficacy in animal models of fibrosis (162). Nintedanib is a multi-receptor tyrosine kinase inhibitor that primarily targets receptors for vascular endothelial growth factor, fibroblast growth factors, and platelet-derived growth factors, which are important drivers of fibrosis in the lung (163, 164). Combination chemotherapeutic strategies that include nintedanib have demonstrated a survival benefit in cancer (165). Other antifibrosis drugs are in preclinical and early clinical trials. For example, αv integrin inhibitors have demonstrated activity in fibrosis models (166).

With increasing tumor stiffness, intratumoral blood and lymphatic vessels compress and eventually close, which causes interstitial fluid to accumulate, generate increased pressure, and reduce efficient drug transport across blood vessel walls (167). These findings provide a compelling rationale to alleviating tumor stromal stiffness as a means of improving drug delivery. On the basis of evidence that depleting CAFs or collagen can reduce tumor stiffness (167), preclinical studies were performed with a sonic hedgehog inhibitor to target CAFs or with antifibrotic agents (e.g., pirfenidone, losartan, tranilast, or hyaluronidase), which improved tumor perfusion, drug delivery, and treatment efficacy (167–169). On the basis of these findings, a phase II clinical trial with losartan and FOLFIRINOX is under way in pancreatic cancer (ClinicalTrials.gov, NCT01821729).

Efforts are also under way to target collagen-modifying enzymes. Neutralizing antibodies against LOX or LOXL2 have efficacy in preclinical cancer models (93, 121, 170–176), but clinical trials that combined anti-LOXL2 antibodies with chemotherapy failed to show increased efficacy (177, 178). These approaches may have failed because of early metastatic escape, which has been reported in pancreatic ductal adenocarcinoma (179). Minoxidil has been used to inhibit LH2 in preclinical models (180), but its mode of action is unclear. LH2 might also be targeted indirectly with tacrolimus, which inhibits FKBP65, a peptidyl prolyl isomerase that enhances LH2 enzymatic activity (79, 80). Developing selective inhibitors of collagen-modifying enzymes will require insight into the structural properties of their active sites, but crystal structures of these enzymes have not been reported.

Genetic and pharmacologic strategies to deplete CAFs in genetically engineered mouse models of cancer have yielded disparate outcomes. In pancreatic cancer models, disruption of sonic hedgehog/smoothened-dependent signaling in fibroblasts prolonged survival and chemotherapy responsiveness in one study (181) and accelerated cancer progression in another (182). Genetic depletion of proliferating αSMA+ myofibroblasts in pancreatic cancer models substantially decreased myofibroblasts and fibrosis (183), and the CAF-depleted tumors displayed a more aggressive phenotype and alterations in regulatory T cells that increased responsiveness to anti-CTLA4 therapy, raising the possibility that CAF-targeting strategies may have both beneficial and detrimental effects. In an alternative therapeutic concept, CAFs can be reprogrammed to a normal fibroblast-like state that suppresses tumorigenesis (4, 138, 184). Supporting this concept, agonists of the vitamin D receptor, a master regulator of pancreatic and hepatic stellate cells (184), inhibit stromal fibroblasts in pancreatic cancer and combine with gemcitabine to dramatically reduce tumor size. Similar findings were observed when all-trans retinoic acid was used to reverse pancreatic stellate cell activation, which also caused profound increases in cytotoxic T cell infiltration into tumors (144). Macrophage activation by CD40 agonists led to depletion of the fibrotic matrix and active tumor cell killing (185), suggesting that immune strategies may have the beneficial secondary effect of reversing tumor-associated fibrosis.

Summary

Recent findings show that fibrosis plays a central role in regulating the hallmark features of cancer. However, large gaps in this understanding remain and must be addressed in order to develop a comprehensive model that can be used to selectively target CAF populations and ECM molecules for the purpose of arresting tumorigenesis and metastasis, the key driver of cancer-related mortality.
Acknowledgments

This work was supported by the NIH through R01 CA105155 (to JMK and MY), R01 HL127283 (to THB), R01 HL132585 (to THB), and R21 AR060978 (to MY); and by Cancer Prevention Research Institute of Texas Multi-investigator Research Awards RPI20713 (to JK and DLG) and RPI60652 (to JK and JMK). JMK holds the Elza A. and Ina S. Freeman Endowed Professorship in Lung Cancer. DLG is an R. Lee Clark Fellow of the University of Texas MD Anderson Cancer Center supported by the Jeane F. Shelby Scholarship Fund.

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