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# The role of the myofibroblast in tumor stroma remodeling

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**Abbreviations:** α-SMA, α-smooth muscle actin; BM, bone marrow; CGTF/CCN2, connective tissue growth factor; ECM, extracellular matrix; EGF, epidermal growth factor; EMT, epithelial-to-mesenchymal transition; FGF, fibroblast growth factor; FN, fibronectin; HSC, hepatic stellate cell; HGF, hepatocyte growth factor; LAP, latency-associated protein; LOX, lysyl oxidase; LTBP-1, latent TGFβ1 binding protein 1; MMP, matrix metalloproteinase; MSC, mesenchymal stem cell; PDGF, platelet-derived growth factor; SLC, small latent complex; SM, smooth muscle; TGFβ, transforming growth factor-beta; TIMP, tissue inhibitor of MMP; TNF, tumor necrosis factor; VEGF, vascular endothelial growth factor



Since its first description in wound granulation tissue, the myofibroblast has been recognized to be a key actor in the epithelial-mesenchymal cross-talk that plays a crucial role in many physiological and pathological situations, such as regulation of prostate development, ventilation-perfusion in lung alveoli or organ fibrosis. The presence of myofibroblasts in the stroma reaction to epithelial tumors is well established and many data are accumulating which suggest that the stroma compartment is an active participant in tumor onset and/or evolution. In this review we summarize the evidence in favor of this concept, the main mechanisms that regulate myofibroblast differentiation and function, as well as the biophysical and biochemical factors possibly involved in epithelial-stroma interactions, using liver carcinoma as main model, in view of achieving a better understanding of tumor progression mechanisms and of tools directed toward stroma as eventual therapeutic target.

## Introduction

Tissue-resident stromal cells, often loosely defined under the term "fibroblast," form the extracellular matrix (ECM) supportive scaffold of connective tissues during development and maintain the stroma in the adult organism. In conditions of disturbed tissue homeostasis, such as occurring after injury during wound healing, chronic inflammation or upon transformation of adjacent epithelium in cancer, stromal cells become activated to proliferate and upregulate ECM production. A central feature of activated stroma cells is the acquisition of smooth muscle (SM) features, most notably neo-formation of contractile stress fibers and expression of α-SM actin (α-SMA); hence the name of myofibroblast. The transient acquisition of this phenotype is beneficial for normal tissue repair processes when myofibroblast remodeling activities restore and preserve tissue integrity. However, persistence of myofibroblasts result in tissue stiffening and deformation.[1] In fibrosis, stiff scar tissue alters normal organ function; during the stroma reaction to epithelial tumors, the mechanical and chemical conditions generated by myofibroblasts promote tumor progression. The resemblance between tumor formation and normal wound healing has often been stressed.[2,3] We here develop that, in fact, the stroma environment altered by tumors resembles fibrotic tissue in many aspects. Most evidently, similar to fibrotic contractures, "healing" does not stop in the tumor environment. After elaborating on similar features between these two pathological conditions, we use liver cancers as an example to highlight that fibrosis is not only associated with tumor development but can be a neoplastic risk factor.

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## The Stroma of Normal Organs

**The stromal ECM.** Traditionally, the stroma of different organs is described as a structural scaffold dominated by ECM with sparsely embedded cells. The stroma ECM includes different types of collagens, elastin, fibronectin, hyaluronic acid, proteoglycans and glycoproteins.[4] In addition to playing important roles during development[5] and in maintaining tissue architecture, ECM components can modify the activity of growth factors and cytokines. The ECM can act as a reservoir for growth factors that are deposited and can be rapidly released upon cellular request.[6,7] ECM molecules protect growth factors from degradation and provide biological latency.[8] For example, latency and activation of transforming growth factor-β1 (TGFβ1) is orchestrated by binding to the fibrillin protein family member latent TGFβ1

binding protein-1 (LTBP-1), decorin or thrombospondin-1.[9-11] Vascular endothelial growth factor (VEGF) also binds to heparin or proteoglycans, and release of VEGF by plasmin or heparanase triggers endothelial cell proliferation.[12] The importance of maintaining ECM homeostasis becomes evident during aging when ECM synthesis and degradation get out of balance. With age, structural and functional changes in components of the dermal-epidermal junction result in a less effective epidermal anchoring system.[13] The synthesis of type I and III collagen is decreased in fibroblasts of the elderly;[14] this is accompanied by decreased levels of TGFβ1 and the downstream mediator connective tissue growth factor (CTGF/CCN2). It has been suggested that reduced activity of the TGFβ1/Smad/CCN2 axis mediates reduced type I procollagen expression in aged human skin.[15] In contrast, fibroblasts of aged connective tissue produce higher levels of collagen-degrading enzymes than those in young tissue. Since fibroblasts cannot properly adhere to fragmented collagen, they seem to lose the ability to mechano-sense the properties of their scaffold ECM.[16]

**Origins and roles of cells in the stroma of normal organs: all fibroblasts?** Organs rely on the migration, proliferation and secretory activity of stromal cells that generate the ECM composition essential for normal tissue homeostasis and physiology.[17] To maintain these functions in the adult organism, connective tissue cells must be renewed. Traditionally, the term fibroblast is often used synonymously for stromal cells; however, it becomes increasingly clear that the stromal cell population is tremendously heterogeneous and of multiple origins. Local and circulating stem cells are among a variety of progenitor cells that have been identified to regenerate the stroma.[18,19] Local mesenchymal stem cells (MSCs), also called mesenchymal stromal cells,[20] are present in most human adult tissues.[21,22] The dermis of the skin for example is hosting resident MSCs;[23] adipose precursor cells regulate skin stem cell activity.[24] Multipotent adult stem cells with the ability to generate both neural and mesodermal progeny, coined skin-derived precursors, have also been identified and isolated from the skin.[25,26] Skin-derived precursors are neural crest-related precursors that migrate into the skin during embryogenesis, persist in a dermal niche, and play key roles in physiology and potentially pathology of the skin.[27] In addition, perivascular cells, generally referred to as pericytes, which are associated with blood vessels, also provide a reservoir of multipotent progenitor cells.[28] Pericytes obtained from various human organs, including skeletal muscle, pancreas, adipose tissue, umbilical cord and placenta, exhibit osteogenic, chondrogenic and adipogenic potentials, i.e., features of MSCs.[29,30]

Another possible but debated source for the local stroma cell population is epithelial cells that undergo epithelial-to-mesenchymal transition (EMT). EMT is defined as the process through which epithelial cells, including endothelial cells, lose their traits and gain features associated with mesenchymal cells.[31] Epithelial cells, which form the lining of glandular organs, normally exist as sheets of polarized cells with tight intercellular and cell-basement membrane junctions. During EMT, epithelial cells dissociate these junctions, start to migrate independently and invade the ECM.[32] EMT facilitates a number of physiological processes, such as normal wound healing, as well as of pathological situations, such as fibrosis and cancer metastasis.[33-36] However, the role of EMT in contributing to normal stroma turnover is unclear.

In addition to local stem cells, bone marrow (BM)-derived and blood-circulating progenitors can participate in the physiological renewal of the stroma.[37] BM-derived stromal cell progenitors include fibrocytes and MSCs. Fibrocytes are characterized by the co-expression of the fibroblast markers collagen type I and II, fibronectin (FN), together with monocyte markers CD13 and CD11b, and hematopoietic progenitor markers CD34, CD45 and CD105.[38,39] They exhibit ECM remodeling properties including the ability to participate in collagen turnover. Due to apparent differences in the collagen and proteoglycan expression profiles between fibrocytes and fibroblasts, it has been proposed that fibrocytes predominantly fulfill an ECM-stabilizing function.[40] Circulating BM-derived MSCs are generally identified by the combined expression of specific cell surface proteins such as CD105, CD90, CD44, CD73, CD166, CD29, CD106 and Stro-1.[41-43] In contrast to fibrocytes, MSCs are negative for the monocyte surface proteins CD13 and CD11b and the hematopoietic markers CD34 and CD45.[44,45] Adult MSCs isolated from BM and expanded in culture are able to differentiate into a number of mesenchymal phenotypes, including those that form bone, cartilage, muscle, fat and other connective tissues.[46] It has been shown that adipocytes can originate from BM-derived circulating progenitor cells, indicating mesenchymal transition as a contributor to homeostatic stroma maintenance.[47] Whereas the contribution of MSCs in pathological situations is beginning to be understood, their contribution and specific roles in maintaining homeostasis of normal stroma remain large elusive.

## The Cancer Stroma: Similarities with Physiological and Pathological Tissue Repair

**Loss of epithelial homeostasis is a common trigger for the stroma reaction against tumors and for normal wound healing.** To describe and understand the cellular and molecular processes involved in cancer development, the analogy with healing wounds is often stressed.[2,3] In wounded skin and epithelialized organs, disruption of the epithelium is often accompanied by dysfunction of the underlying connective tissue.[48] This effect of lost homeostasis is analogous to the influence that neoplastic epithelium has on the surrounding stromal cells. The disturbed interaction between neoplastic cells and the surrounding connective tissue confers to the stroma component its peculiar features.[49] Schauer and Rowley, among others, have recently supported the concept that injury changes the priority of cell behavior: "…it is becoming very clear that the stromal compartment response to acute wound repair in adult tissue is governed by a biology of priority, beginning when the epithelial layer is breached. Host response mechanisms within repairing tissue follow a repair-centric biology of priority, as compared with a developmental biology of priority, as factors, mechanisms and the cell/tissue biology is different in many ways."[50]

An important element in cancer progression is the cross-talk between the transformed epithelium and stromal cells. Examples

from embryonic development highlight the influence that the stroma or mesenchyme has on epithelial behavior. During development of the prostate, the urogenital sinus mesenchyme fulfills a number of regulatory functions: it specifies prostatic epithelial identity, induces epithelial bud formation, elicits prostatic bud growth and regulates ductal branching, promotes differentiation of a secretory epithelium, and specifies the types of secretory proteins expressed.[51,52] Reciprocally, prostatic epithelium induces SM differentiation in the mesenchyme. The central role of mesenchyme in prostatic epithelium development has been elegantly demonstrated by analyzing tissue recombinants composed of androgen-receptor-positive wild-type mesenchyme and androgen-receptor-negative epithelium.[53] These studies revealed that ductal morphogenesis, differentiation, apoptosis and proliferation of epithelial cells are all regulated by stromal and not epithelial androgen receptors.[53,54]

The mammary gland is another excellent model to understand the function of stromal-epithelial interactions. It has been shown that TGFβ1, a major inducer of ECM deposition, acts during mammary gland development but also in a variety of developing tissues to mediate epithelial-mesenchymal interactions.[55] This notion is supported by the immunohistochemical localization of TGFβ1 in numerous mouse embryonic tissues at sites where epithelial-mesenchymal interactions is occurring.[56] Moreover, the normal human mammary gland undergoes a well-defined sequence of histological changes in both epithelial and stromal compartments during the menstrual cycle. In this process, the ECM surrounding individual cells plays a central role in modulating cell proliferation, differentiation and gene expression. Hence, stroma-derived ECM molecules may act as mediators in the hormonal control of the mammary gland in addition to their structural role.[57] It has also been shown that mammary epithelial-mesenchymal interactions influence the alternative splicing of FN, which plays a key role in cell adhesive and migratory behavior related to fundamental processes such as embryogenesis and maintenance of tissue integrity, but also wound healing and malignancy.[58,59] Interestingly, in the mammary gland, strategically positioned cells of the myoepithelial lineage are implicated in the phenomenon of menstrual cycle-related growth spurts in the adult resting breast. These myoepithelial cells mediate the complex signaling pathways involved in local epithelial-mesenchymal interactions, and which are crucial for both orderly growth during development and maintenance of homeostasis in the adult.[60] In the adult organism, epithelial-mesenchymal interactions play a role in tissue homeostasis by reciprocally maintaining epithelial and stromal differentiation and growth-quiescence.[61]

**Parallels between the evolutions of cancer and wound healing.** Acute injuries heal in a highly regulated sequence of overlapping processes that require the coordinated completion of a variety of cellular activities.[62,63] Wound healing phases include (1) vascular constriction and fibrin clot formation; (2) invasion of inflammatory cells into the wound and release of pro-inflammatory cytokines and growth factors;[64] (3) a proliferative phase which is characterized by granulation tissue formation and re-epithelialization; and (4) the ECM remodeling phase during which the remaining inflammatory, vascular and fibroblastic cells die by apoptosis.

In normal wound healing, platelets are a major source of pro-inflammatory growth factors and establish the provisional fibrin ECM. A recent study suggested that platelets prime metastasizing tumor cells toward a mesenchymal phenotype already in the circulation by providing them with active TGFβ1 and by physical interaction.[65] In the local tumor stroma, platelets and other blood-derived hematopoietic cells are rich sources for a variety of growth factors. In addition, these cells[66] together with tumor cells release plasma-membrane-derived microparticles which contribute to the activation of cancer-associated myofibroblasts.[67] Although vessels are generally not damaged in cancer, they become hyperpermeable and permit leakage of plasma proteins, fibrinogen and FN into the stroma.[68] The cross-linked fibrin ECM is rich in plasma- and inflammatory cell-derived growth factors; this is strikingly similar to the ECM of developing cancer.[3,69] The predominant factors are cytokines of the fibroblast growth factor (FGF) family, platelet-derived growth factor (PDGF), tumor necrosis factor (TNF)-α, epidermal growth factor (EGF), hepatocyte growth factor (HGF), TGFβ1 and VEGF.[70,71] In acute wounds, the formation of reactive stroma starts approximately four days after injury, when macrophages, endothelial and fibroblastic cells invade the wound space. It is clear that chronic inflammation and different inflammatory cells contribute to cancer development.[72,73] Macrophages augment inflammatory responses and additionally secrete VEGF and FGF, which promote angiogenesis.[74] The formation of numerous new capillaries confers to the stroma a granular appearance. Neovascularization is essential for the synthesis, deposition, and organization of a new ECM. Moreover, FGF, TGFβ1 and PDGF cause fibroblast infiltration and activation into contractile myofibroblasts, which dominate the proliferation and remodeling phases of wound healing.

After the inflammatory phases, the wound repair process is characterized by significant migration into the injured zone, proliferation and activation of quiescent precursor cells and their activation into myofibroblasts, which then leads to wound contraction and ECM remodeling (**Fig. 1**).[74] Initially, fibroblastic cells utilize the fibrin cross-linked fibers formed by the end of the inflammatory phase to migrate across the wound, subsequently adhering to FN. Fibroblastic cells then progressively transform in myofibroblasts which deposit collagen (mainly collagen type III) into the wound bed, leading to the formation of a sophisticated ECM network to which they can adhere, permitting their migration, and allowing the final formation of the granulation tissue. Both their precursor cells and activated myofibroblasts are responsible for the production of ECM components, including collagens and elastin, which give the ECM strength and resilience. They also synthesize highly hydrated molecules, such as proteoglycans and glycosaminoglycans. This ECM regulates cellular functions via cell adhesion and migration, also providing a storage and diffusion system for signaling molecules, ions, hormones, nutrients and waste products.[63]

When normal healing wounds are closed and re-epithelialized, cellularity within the granulation tissue decreases due in part to myofibroblast and endothelial cell apoptosis.[75] The additive effect of reduced growth factor expression, increased ECM turnover, and nitric oxide generation may result in the myofibroblast and

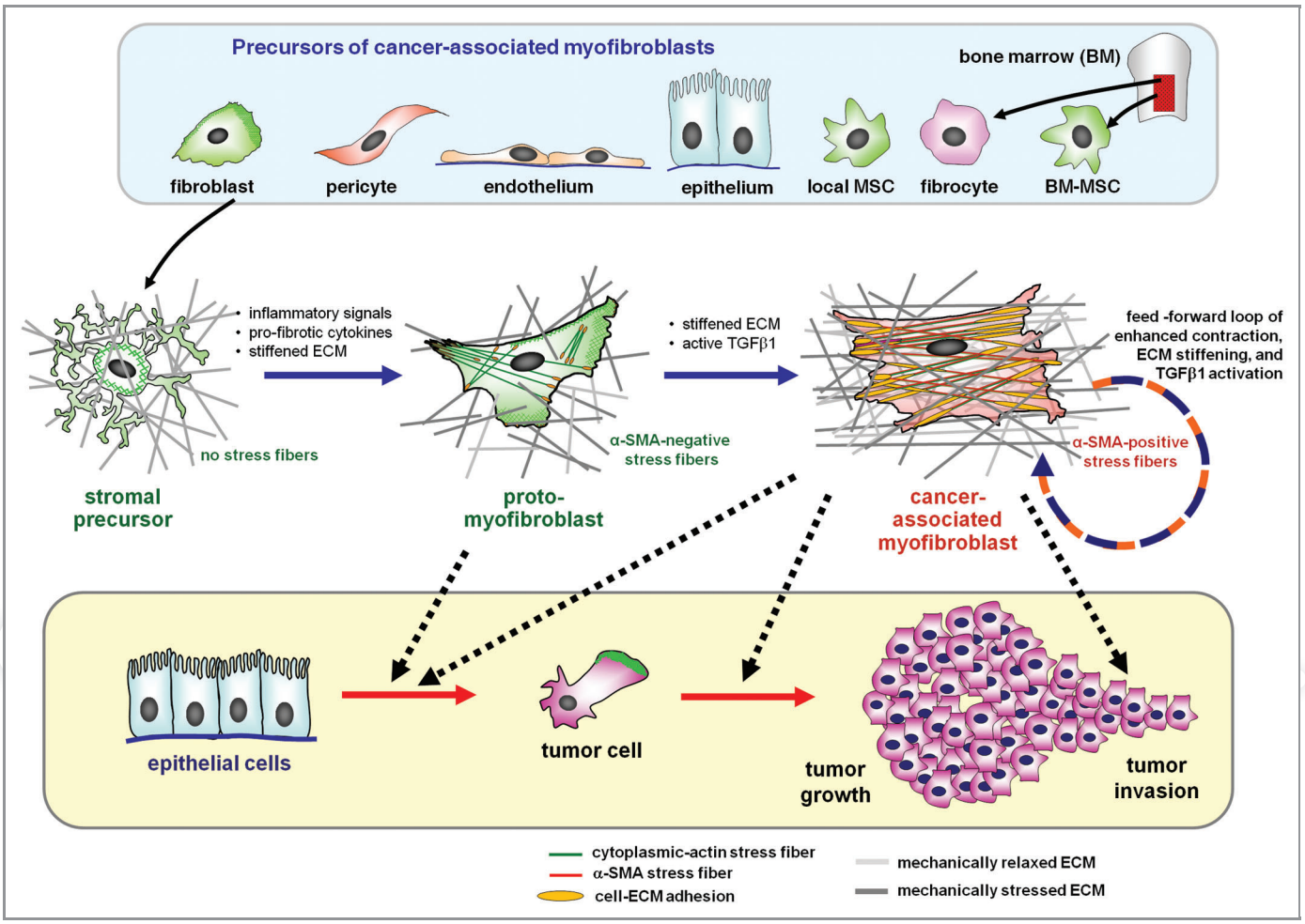


**Figure 1.** The myofibroblast in the tumor stroma. Myofibroblasts associated with the tumor stroma can be activated from a variety of different progenitor cells, including locally residing fibroblasts, epithelial and endothelial cells via epithelial-to-mesenchymal transition, pericytes and bone marrow-derived circulating fibrocytes and mesenchymal stem cells (MSCs). In the intact tissue, the precursor cells are stress-shielded by a functional extracellular matrix (ECM); they do not develop contractile features and cell-matrix adhesions. Upon injury and loss of tissue homeostasis inflammatory signals activate stromal cells to spread and remodel the initially soft ECM. The gradual increase in ECM stiffness permits the formation of contractile microfilament bundles of cytoplasmic actins (stress fibers) that characterize the proto-myofibroblast. Transforming growth factor-β1 (TGFβ1) in conjunction with the stiff ECM stimulates proto-myofibroblasts to express and incorporate α-smooth muscle actin (α-SMA) into stress fibers. The force generated by α-SMA-containing stress fibers leads to further ECM contraction, thereby establishing a mechanical feedback loop. The chemical and mechanical environment created by proto-myofibroblasts and differentiated myofibroblasts support epithelial cell transformation, invasion and tumor growth.

vascular cell apoptosis seen during the rapid remodeling of this tissue.[76] Beside normal scar formation, hypertrophic scarring occurs in some circumstances, such as in young burn patients. Hypertrophic scarring leads to severe functional and aesthetic defects[77] caused by the numerous α-SMA expressing and contracting myofibroblasts.[78] Interestingly, in fetal wounds, healing can occur without scarring or contracture.[79] This ability is lost in late gestation. In vivo, early fetal wounds show markedly fewer α-SMA-positive myofibroblasts than in late fetal wounds or in adult wounds where they are abundant.[80]

For wounds to heal successfully, all phases must occur in the proper sequence. Any factors interfering with one or several phases of this highly regulated process can cause impaired (chronic wounds) or overly (fibrosis and hypertrophic scarring) wound healing.[81] Tumor growth induces an abnormal and prolonged stromal reaction leading to excessive scarring not unlike hypertrophic cutaneous scars observed after severe acute injury such as severe burns.[49] One of the major players in creating hypertrophic scars or connective tissue deformations in general is the myofibroblast, the predominant phenotype of cancer-associated fibroblasts.

## The Role of Myofibroblasts in the Cancer Stroma

**Definition of the myofibroblast.** At the time of their discovery in normally healing wound granulation tissue, myofibroblasts have been described as fibroblasts that are specialized for ECM secretion and contraction.[82] The term myofibroblast was chosen to acknowledge the co-existence of fibroblast morphological features, such as a developed endoplasmic reticulum and SM features such as contractile actin microfilament bundles.[82] This

functional and morphological definition is still valid as of today as their most basic but also most essential characterization.[83] Myofibroblast activation comprises two phases, each of which is characterized by specific cytoskeletal features. (1) De novo acquisition of contractile bundles that generate sufficient forces to promote cell migration and to initially remodel the ECM.[84] For these lower contractile cells, we have introduced the term "proto-myofibroblast."[1] (2) In the presence of mechanical stress and TGFβ1, proto-myofibroblasts can further differentiate into myofibroblasts that neo-express α-SMA in stress fibers.[1] It is the incorporation of α-SMA into stress fibers that renders myofibroblasts highly contractile (**Fig. 1**).[85] By strict definition, cells that express α-SMA but do not incorporate it into contractile microfilament bundles cannot be functional myofibroblasts. In standard cell culture, during which fibroblastic cells almost inevitably form stress fibers, the term "myofibroblast" generally describes cells expressing α-SMA in contractile microfilament bundles.

Neo-expression of α-SMA is the most widely used criterion to identify tissue myofibroblasts and to diagnose myofibroblast-related diseases. Using α-SMA expression as marker, myofibroblasts have been shown to be the predominant sub-population of cancer-associated fibroblasts in the tumor stroma.[86,87] In the complex environments of healing wounds and tumors, α-SMA cannot be used as a unique myofibroblast identifier. Vascular SM cells populating the tumor stroma and wound granulation tissue are also α-SMA positive. However, SM cells express late muscle differentiation markers that are rarely expressed by myofibroblasts, including SM myosin heavy chain, h-caldesmon and smoothelin.[88] The muscle intermediate filament protein desmin is another reliable exclusion criterion because it is expressed in myofibroblasts only in exceptional situations.[88] It is equally difficult to distinguish between myofibroblasts and pericytes, which can express vimentin and desmin, are α-SMA positive and SM myosin negative but which generally lack contractile features in vivo, i.e., stress fibers.[89,90] The fact that the myofibroblast shares features and markers with many other cell types raises the interesting question whether it should be regarded as a cell type or a phenotype. Indeed, myofibroblasts derive from a variety of different precursor cells (**Fig. 1**) further indicating that "myofibroblast" designates a collection of cells that may be as heterogeneous as the "fibroblast." We will use the general term "cancer-associated myofibroblast" to summarize this heterogeneous population.

**Origins of myofibroblasts in cancer and fibrosis.** Many elegant cell tracing studies have been performed to identify the source(s) for α-SMA positive myofibroblasts in different conditions of injury, fibrosis and tumor development.[91] To date, it is probably safe to state that our body opportunistically activates myofibroblasts from whatever sources are available in a given condition. In response to injury and disturbed tissue homeostasis, local fibroblasts have been shown undergo myofibroblast activation in skin,[92] liver,[93-95] lung,[96-98] heart,[99-101] kidney[102] and in the stroma reaction to epithelial tumors.[103-106] EMT is another mechanism of myofibroblast generation from local epithelial and endothelial precursors during tumor development,[107-109] as well as in kidney fibrosis[110] and lung fibrosis.[111,112] EMT has been demonstrated to contribute to fibrosis of the heart[113] and liver.[114,115] In fibrotic liver, hepatic stellate cells (HSCs) are another important source of myofibroblasts.[93,95] In addition, de-differentiation of SM cells into ECM synthesizing cells contributes to the myofibroblast population.[116] In the tumor stroma, systemic sclerosis, vessel repair and dermal scarring, pericytes have been suggested to acquire contractile myofibroblast features.[89,117]

Additional possible sources for cancer-associated myofibroblasts are BM-derived, blood-circulating fibrocytes and MSCs, which are recruited to inflamed and remodeled tissue. BM-derived cells have been associated in varying numbers with myofibroblast-containing lesions in the context of tumor development[118,119] and in animals subjected to fibrotic stimuli in a variety of different organs.[118,120-131] Other studies seem to exclude that BM-derived fibrocytes contribute to myofibroblast formation in liver[124] and lung fibrosis[132] and the definitive answer to the question of fibrocyte-to-myofibroblast differentiation remains open. Circulating and transplanted MSCs have been shown to target to the stroma environment of epithelial tumors.[117,133-136] This tumor homing property has been suggested to be exploited for the tumor-specific delivery of anti-cancer drugs, cytokines and viruses[137,138] and to suppress tumor development.[139] However, the tumor environment seems to activate MSCs to myofibroblasts similar to other precursor cells.[117,140,141] BM-MSCs cultured in tumor-conditioned medium differentiate into α-SMA-positive myofibroblasts.[142] Recent studies evaluating the interaction between MSCs and epithelial tumor cells in vivo and in vitro indicate that acquisition of the myofibroblast phenotype by MSCs can reduce the success of an envisaged MSC therapy and may even amplify the disease. MSCs that have become activated by mildly invasive human breast carcinoma cells in culture enhance the metastatic potential of the cancer cells when injected subcutaneously; this effect is mediated in a paracrine feedback loop.[143] In contrast, other studies did not confirm myofibroblast activation of BM-MSCs in the tumor environment[117,144] and the contribution of BM-derived MSCs to the myofibroblast population remains a matter of debate.[145,146]

**Mechanisms of myofibroblast activation: The role of TGFβ1.** Independent from the identity of their precursors, myofibroblast activation is promoted by few essential factors. We will here focus on TGFβ1, the most potent myofibrogenic growth factor, and on mechanical stress. Both factors have substantial influence on tumor development and progression and recent studies have demonstrated their close interdependence.[147] TGFβ1 has long been recognized as a key molecule implied both in wound repair and tumor formation.[148] Although many biological effects of TGFβ1 are per se beneficial for the organism, the same actions are used and diverted by tumor cells to spread the disease.[149] Beneficial functions of TGFβ1 in normal tissues include maintaining homeostasis of adult tissues by controlling proliferation of epithelial cells, endothelial cells, immune cells and fibroblasts.[150-152] The fact that cancer cells become insensitive to the growth-arresting action of TGFβ1, together with its pro-angiogenic effects and its potential to inducing EMT of cancer cells, allocates to TGFβ1 a central role in tumor development.[153-155] TGFβ1 causes the disruption of cell-cell junctions

between vascular endothelial cells and thereby facilitates extravasation of metastasizing tumor cells.[156] Blocking the TGFβ1 responsiveness of tumor cells has metastasis-suppressing effects.[157,158] TGFβ1 further exerts pro-fibrotic and pro-tumorigenic activities by mediating the inflammatory response, causing excessive ECM production, decreasing synthesis of matrix metalloproteinases (MMPs), and increasing the synthesis of tissue inhibitors of MMPs (TIMPs).[159] TGFβ1 further promotes myofibroblast activation and survival[92,160-165] and enhances the retention of hyaluronan in the ECM that positively feeds back on myofibroblast activation.[166,167] It appears that the temporal and spatial availability of TGFβ1 to tumor and stromal cells determines whether it acts as a suppressor or promoter of cancer progression and metastasis.[65,152,155]

The time and local availability of TGFβ1 partly depend on the cellular source. In the circulation, platelets have recently been shown to supply metastasizing tumor cells with bioactive TGFβ1.[65] Other prominent sources of TGFβ1 in the tumor environment are the transformed epithelium itself, inflammatory, vascular and fibroblastic stroma cells.[155,168] Myofibroblasts strongly contribute to the production and activation of TGFβ1 in the activated stroma and thereby generate the autocrine feed-forward loop that is characteristic for persisting myofibroblast activities,[169] similar to those observed in fibrosis. Given the pleiotrophic effects of TGFβ1, different strategies are currently pursued to inhibit TGFβ1 action in a cell-specific manner in addition to general blocking approaches.[170,171] The recent findings of a contraction- and integrin-mediated TGFβ1 activation mechanism acting in myofibroblasts may provide novel tools to achieve this goal.[172] TGFβ1 is synthesized together with its pro-peptide, the latency-associated peptide (LAP) which is intracellularly cleaved but remains associated with TGFβ1 to produce the small latent complex (SLC).[173] Myofibroblasts and other cells secrete SLC in a large latent complex with the covalently bound LTBP-1 (**Fig. 2**).[173,174] LTBP-1 is a member of the fibrillin protein family and stores latent TGFβ1 in the ECM where it is accessible for cell-mediated activation.[8,10,11] Activation of latent TGFβ1 from ECM deposits involves dissociation from LAP and is promoted by a variety of different mechanisms that depend on the cell type and physiological context.[9,173,175,176] Transmembrane integrins have been identified as major players in

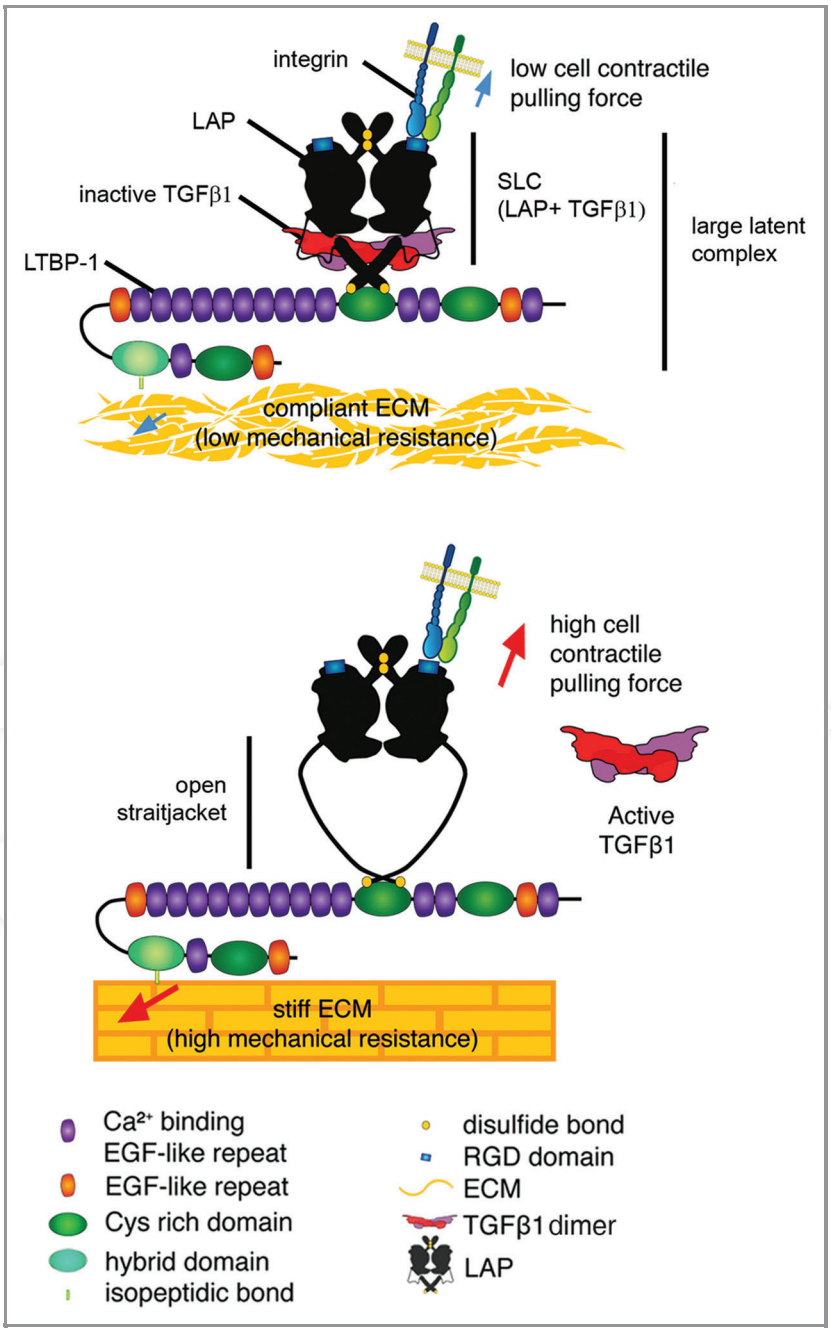


**Figure 2.** Integrin-mediated TGFβ1 activation by cell contraction. Structural and force spectroscopy data suggest that the transforming growth factor-β1 (TGFβ1) and latent TGFβ1 binding protein-1 (LTBP-1) binding domains of the latency-associated peptide (LAP) act as a sensor in a mechanical model of integrin-mediated TGFβ1 activation. Mechanical stretch, applied through cell integrins will open the latent TGFβ1 complex to release TGFβ1. Flexible domains in the LAP that are prone to unfolding lie within a domain that has been coined "straitjacket."[179] In the context of a poorly organized and compliant matrix and when cells develop only low contractile activity, the lack of sufficient mechanical tension will prevent the integrin-mediated conformational changes that are required to activate TGFβ1 from the latent complex. Conversely, on a stiff matrix the transmission of contractile forces via integrins to the LAP will favor unfolding of the straitjacket region, resulting in TGFβ1 release. Reproduced with permission.[184]

the activation of latent TGFβ1, which contains RGD motifs for integrin binding in the LAP portion.[177-179] Binding comprises all αv integrins (αvβ1, αvβ3, αvβ5, αvβ6 and αvβ8), integrins α5β1, α8β1 and αIIbβ3.[176,180,181] Whereas αvβ8 integrin seems to guide proteases to the latent complex for proteolytic TGFβ1 activation,[175,180,182] integrins αvβ5, αvβ6 and αvβ3 were shown to activate latent TGFβ1 independently from proteolytic action. Notably, all these integrins are upregulated in different fibrotic conditions and in the tumor environment.[176,181]

Different recent studies have demonstrated force-dependent activation of latent TGFβ1.[179,183-188] Together they support the concept that cells, in particular contractile myofibroblasts, can exert tensile forces on ECM-stored latent TGFβ1 via specific integrins to activate the latent cytokine. Consistently, inhibition of myofibroblast integrin binding to LAP using RGD- and LAP-competitive peptides blocks activation of latent TGFβ1 in vitro.[183] A similar effect has been achieved by inhibiting contraction of myofibroblast[183] and epithelial cells.[188] It appears that traction force exerted to the large latent complex induces a conformational change in LAP that liberates active TGFβ1. We have recently measured the mechanical stress involved in TGFβ1 activation at the molecular level and demonstrated TGFβ1 release upon force transmission to LAP.[184] The recently published three-dimensional structure of the SLC[179] and force spectroscopy of large latent complex unfolding[184] support the following mechanism of TGFβ1 activation from the large latent complex (**Fig. 2**): (1) Mechanical force applied to LAP by single integrins can unfold a flexible portion of LAP that traps TGFβ1 in a "straitjacket" conformation. (2) Complete opening of the straitjacket is only possible when LAP is bound to LTBP-1, which must be anchored with the ECM. The ECM needs to be sufficiently stiff to mechanically resist the cell pulling forces. (3) TGFβ1 is released in an all-or-nothing fashion.

Of all protease-independent TGFβ1-activating integrins, the epithelial integrin αvβ6 has been most extensively studied, predominantly in the context of lung fibrosis.[189] Deletion or inhibition of β6 integrin in vivo efficiently protects from the development of experimentally induced lung fibrosis with no apparent side effects.[190,191] The role of this integrin in tumor development is far less clear but it has been suggested that overexpression of αvβ6 stimulates tumor progression by supporting EMT.[192,193] Whether this effect is related to its function in TGFβ1 activation remains elusive. The contribution of integrins that are expressed by myofibroblasts and mesenchymal cells to the activation of latent TGFβ1 in the tumor environment has not been addressed. However, inhibition of the "pro-angiogenic" integrins αvβ3 and αvβ5 has already entered clinical trials as one strategy to interfere with tumor angiogenesis.[194] It will be interesting to investigate if targeting these integrins will also intercept the autocrine loop of myofibroblast differentiation and TGFβ1 activation in the tumor.

**Mechanisms of myofibroblast activation: The role of tissue stiffness.** The second main permissive factor for myofibroblast activation and persistence is mechanical stress that arises from active remodeling activities in the stroma but also from the resulting mechanical properties of the ECM.[1,83] We will here focus on the role of ECM stiffness in myofibroblast activation. It has to be noted that cells actively probe ECM stiffness by exerting pulling forces; higher resistance of their environment to pulling results in higher intracellular stress.[1,83] Stiff ECM promotes myofibroblast phenotypic conversion at several levels,[83] notably by improving the efficiency of latent TGFβ1 activation. Whereas compliant substrates appear to absorb the large deformations generated by myofibroblast contraction and thus protect the latent complex against conformational changes, the complex is stretchable on stiff substrates.[183] It is a well established fact that the cancer-associated stroma is stiffer than the surrounding normal soft connective tissue.[195-199] This mechanical condition is clinically exploited to detect tumors by palpation and/or elastography.[200-202] The migratory activity of activated stromal cells and the high contractile activity of myofibroblasts are instrumental in gradually increasing ECM stiffness in more advanced stages of the stroma reaction.[83] Initial stiffening however seems to be promoted by other processes. Small changes in tissue stiffness occur during the inflammatory response in fibrosis and tumor development and seem to be induced by cross-linking of collagen by lysyl oxidases (LOX) and LOX-like enzymes; inhibition of these enzymes has tumor-suppressing effects.[203-206] Another cause for "pre-stiffening" in the tumor environment can be high interstitial fluid pressure and increased lymphatic flow.[207,208] Using three-dimensional collagen co-cultured of fibroblasts and tumor cells, it has been shown recently that even very low interstitial fluid flow can lead to ECM and fibroblast alignment and subsequent myofibroblast differentiation.[209] This process is associated with upregulated levels of TGFβ1.[210]

Tissue stiffness is measured as Young's modulus in units of pascal and high stress is required to deform materials with high Young's modulus. The stiffness of normal soft organs usually ranges between 2–15 kPa when measured at the cellular level using atomic force microscopy; skin and mammary gland tissue are situated at the lower stiffness range with 0.2–5 kPa.[211,212] During the remodeling processes occurring in normal repair, fibrosis and tumor development, ECM stiffness gradually increases and can reach Young's moduli of 50–100 kPa in mature scar tissue. Notably, fibrotic scar tissue is always stiffer than the texture of the normal organ.[213-216]

A great variety of different in vitro systems have been developed to study stiffness-dependent cell behavior in two and three dimensions.[83,217-222] Since this field of mechanobiology literally exploded over the last decade, we will here only briefly summarize studies addressing myofibroblast activation by exposure to stiff substrates. By growing fibroblasts on very soft two-dimensional polyacrylamide gels and in three-dimensional soft collagen gels, development of stress fibers and acquisition of the proto-myofibroblast phenotype is suppressed; α-SMA stress fibers are beginning to be developed in cells grown isolated on culture substrates exhibiting an elastic modulus of at least 3 kPa.[221,223] Stiffer culture substrates with a Young's modulus of $> 20$ kPa are required to permit further myofibroblast differentiation and expression of α-SMA.[213-215] In three-dimensional setups, myofibroblasts express α-SMA in attached stressed collagen gel cultures but not in free-floating relaxed gels.[224-226] In mechanically

challenged rat skin wounds, expression of α-SMA is accelerated; releasing wounds from mechanical tension has the opposite effect.[84] Similar results have been obtained by stretching human burn scar tissue in situ.[227] The level of stress exerted by the stiff ECM and/or dynamic changes in stress are also important signals for myofibroblast survival and thus their persistence. Increased apoptotic figures have been reported for fibroblasts in stress-released collagen gels[228] and experimentally relaxed wounds.[229] Conversely, mechanically stressing dermal wounds in mice causes hypertrophic scarring, presumably by decreasing the rate of apoptotic myofibroblasts.[230]

**Consequences of myofibroblast activation in the tumor stroma.** Activation of stromal cells into cancer-associated myofibroblasts has many consequences for tumor development, progression and cancer metastasis. Although their myofibroblast phenotype has not always been considered in the respective studies, activated cancer-associated fibroblasts have been reported to produce a variety of growth factors and cytokines that promote tumor progression. Secreted stroma-derived factors include TGFβ1, HGF, EGF, VEGF, stroma-derived factor-1, basic FGF and the pro-inflammatory cytokines CXCL14, IL-1, IL-6 and IL-8.[105,231,232] Moreover, cancer-associated myofibroblasts contribute to ECM remodeling and foster cancer cell invasion by producing MMPs and TIMPs, such as MMP-1, MMP-2, MMP-3, MMP-9, MMP-13 and MMP-14.[233] Further, cancer-associated myofibroblasts are the main producers of the tumor-surrounding ECM by secreting the matricellular protein CCN2, collagens, tenascin C, FN and elastins.[107,155]

In addition to altering the chemical composition of the stroma, the mechanical responsiveness of myofibroblasts and their role in ECM remodeling and stiffening has important implications for tumor progression.[199] Enhanced tissue stiffness not only feeds back positively on the activation of cancer-associated myofibroblast but seems to increase the risk and invasiveness of tumors. For breast cancers, a clear correlation exists between the degree of mammographic densities (compact and stiff tissue) and the risk of cancer formation.[234,235] Cell culture studies demonstrated that substrate stiffness directly governs the behavior and differentiation of murine mammary epithelial cells. On culture substrates that mimic the softness of normal mammary gland tissue (0.2 kPa), these cells form polarized acini surrounded by an intact basement membrane. This structure resembling the in vivo structure of the normal breast ducts is increasingly disturbed with increasing substrate stiffness. On substrates with a stiffness of 5 kPa, reproducing the mechanical conditions of the tumor stroma, lumen formation is inhibited and no surrounding basement membrane is established. As a consequence of the higher substrate stiffness, epithelial cells lose cell-cell adherens junctions and cell polarity to attain a mesenchymal phenotype with distinct stress fibers and increased migratory activity.[195] Physiologically soft ECM was shown to suppress the mitogenic activity of epithelial (and mesenchymal) cells; stiffer substrates induce mitogenesis.[217,236,237] Hence, the stiff ECM generated by the cancer-associated fibroblast/myofibroblast remodeling activities not only impacts the stromal compartment but drives epithelial cells into an invasive and proliferative phenotype, at least in culture. Physical cues by the ECM are not necessarily created by the mechanical properties but can be of topographic nature. Lines of tension and stroma cell-generated ECM tracks serve as guidance cues for collective cancer invasion.[238-242] The pattern and alignment of collagen fibers in the tumor stroma may even find clinical application to assess the predict of human breast cancer patient long-term survival.[243]

## The Tumor Stroma in Liver Cancers

In the following section we present two examples of liver cancer that are frequently associated with fibrotic conditions. In these cases stromal changes and myofibroblast activation clearly enhance the risk of cancerogenesis.

**Hepatocellular carcinoma.** Hepatocellular carcinomas have numerous etiologies, notably chronic B and C virus infection or chronic alcohol abuse. Often, hepatocellular carcinomas arise in livers showing cirrhosis (**Fig. 3A**). Irrespective of the cause, it is in itself a precancerous condition. Depending on the degree of differentiation, the tumor is composed of large anastomosing plates and acini of tumor hepatocytes surrounded by capillaries. Except in rare forms of scirrhous or fibrolamellar hepatocellular carcinoma, tumor stroma is scanty (**Fig. 3C**). Sometimes the tumor is encapsulated. Often, the tumor stroma is mixed with the fibrous stroma of the surrounding cirrhosis. Microscopically, at low magnification, tumor stroma seems to be organized like the connective tissue surrounding the normal liver parenchyma. At high magnification or ultrastructurally, there are important modifications. The vessels surrounding the tumoral plates are not sinusoids, but continuous capillaries with a continuous basement membrane. They contain fewer Kupffer cells than normal liver.[244] The space between endothelial cells and the tumoral hepatocytes does not contain HSCs, but cells expressing myofibroblastic features including expression of α-SMA. The ECM is remodeled with more deposition of collagen, notably collagen type I,[245] fibrillin-1 and de novo expression of elastin.[246] Myofibroblasts are involved in the remodeling of the ECM; they both synthesize ECM[245-247] and degrade ECM with proteinases, like urokinase or MMPs.[248-250] Interactions between malignant hepatocytes and stromal cells are complex. Tumor cells can recruit cancer-associated myofibroblasts locally or by migration from the transdifferentiated stromal cells through multiple mechanisms. Some growth factors or cytokines are involved in activation and recruitment of stromal cells, like TGFβ1 or PDGF.[245] As shown by Leyland and coworkers using non-tumor hepatocytes, degradation of the ECM by the tumor cell proteinases can indirectly activate stromal cells.[251] Conversely, cancer-associated myofibroblasts can enhance tumor invasiveness, notably by expression of HGF[252,253] or by secretion of MMPs.[254]

**Cholangiocarcinoma.** Bile-duct carcinoma (cholangiocarcinoma) is less common than hepatocellular carcinoma. The tumor is composed of tubular adenocarcinoma set in an abundant fibrous stroma. Three main forms are distinguished: intrahepatic or peripheral bile-duct carcinoma (cholangiocarcinoma), hilar adenocarcinoma (Klatskin tumor) and carcinoma of the extra-hepatic bile ducts. Unlike scanty stroma reaction inside

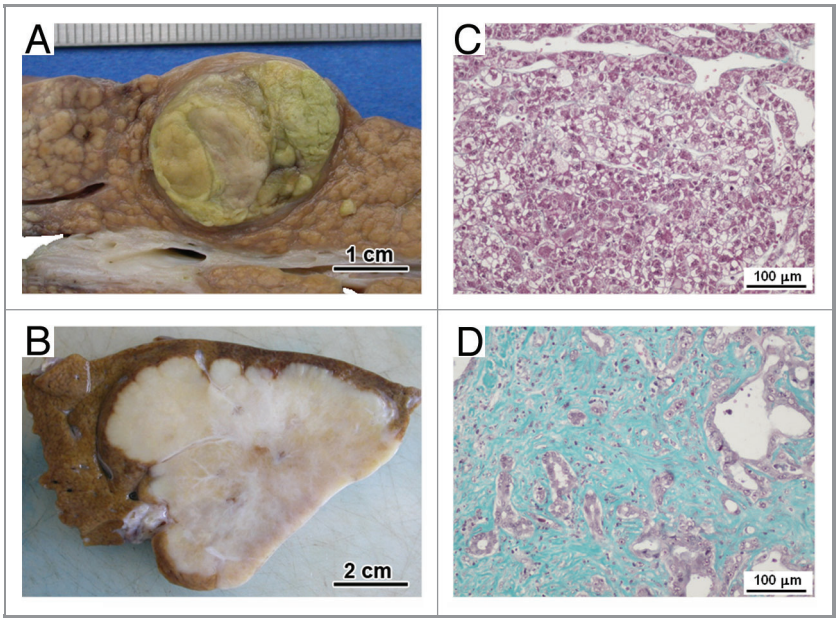


**Figure 3.** Hepatocellular carcinoma and cholangiocarcinoma. Gross appearances of a typical case of hepatocellular carcinoma undergoing on cirrhosis (A) and of a typical case of intrahepatic cholangiocarcinoma showing important hyaline changes (B). The matrix of the tumor stroma is scanty in the hepatocellular carcinoma (C) while in the center of the intrahepatic cholangiocarcinoma, the tumor stroma is fibrous and the tumor cells are inconspicuous (D) (Masson's trichrome histochemistry).

hepatocellular carcinoma tumors, the stroma in cholangiocarcinoma is abundant, sclerous, sometimes with calcification and may be extensive, and submerges the scanty tumoral tubules in cholangiocarcinoma (**Fig. 3B and D**). Inside cholangiocarcinoma tumors, stroma and tumor cells are mixed and there are no clear boundaries between the periphery of the lesion (invasion front) and the inner tumor. The number of cancer-associated myofibroblasts is elevated in the stroma and is correlated with the degree of tumor fibrosis.[255] Around the tumor, α-SMA expressing cells seem in direct continuity with cancer-associated myofibroblasts.[255] These cells are involved in deposition and remodeling of ECM.[256] Stromal cells express MMP-1, MMP-2, MMP-3, MMP-9 or tissue inhibitors of MMPs, TIMP-1 and TIMP-2.[257] This expression of MMPs and TIMPs is stronger in cholangiocarcinomas with severe invasion.[257] Our lab has recently used a proteomic approach to identify differentially expressed proteins in peripheral cholangiocarcinoma cases and compared expression with paired non-tumor liver tissue from the same patients.[258] Overall, of the approximately 2,400 protein spots visualized in each gel, 172 protein spots showed significant differences in expression level between tumor and non-tumor tissue with $p < 0.01$. Of these, 100 spots corresponding to 138 different proteins were identified by mass spectrometry: 70 proteins were overexpressed whereas 68 proteins were underexpressed in tumor samples compared with non-tumor samples. Among the overexpressed proteins, immunohistochemistry studies confirmed an increased expression of 14-3-3 protein in tumor cells while α-SMA, as expected, and periostin were shown to be overexpressed in the cancer-associated myofibroblasts surrounding tumor cells (**Fig. 4**). 14-3-3 proteins have been shown to have roles in suppressing apoptosis or regulating cell survival[259] and may represent a novel indicator of cancer transformation in hepatocytes or biliary epithelium. Periostin is a secreted protein that has integrin binding sites and has been shown to be expressed by tumor cells and tumor stroma in melanoma and colon cancer.[260] Recent examination of fibroblasts isolated from cholangiocarcinoma has shown that these cells are capable of producing periostin and that high levels of periostin production correlate with poor prognosis.[261] Periostin has been shown to induce cell migration and also EMT in pancreatic cancer cells,[262] thus it may represent a novel mediator of tumor growth in cholangiocarcinoma. The detection of periostin or other overexpressed proteins such as 14-3-3 proteins in serum may therefore prove to be useful markers for detection of malignancy.[263]

**Comparison between hepatocellular carcinoma and cholangiocarcinoma.** The question arises why the stroma reaction is scanty in hepatocellular carcinomas and abundant in cholangiocarcinomas. It is conceivable that the cells contributing to the myofibroblastic population and which participate in stroma reaction are different. Myofibroblasts are absent from normal liver. Precursor cells of the myofibroblast in the liver, HSCs and portal fibroblasts, are differently distributed in the hepatic lobule.[264,265] HSCs resemble pericytes and are located along the sinusoids, in the Disse space between the endothelium and the hepatocytes.[266,267] In contrast, portal fibroblasts are embedded in the portal tract connective tissue around portal structures such as vessels and biliary structures. Differences have been reported between these two fibrogenic cell populations, concerning the mechanisms leading to myofibroblastic differentiation, activation and "deactivation."[266-268] It is now widely accepted that the different types of lesions leading to liver fibrosis, e.g., lesions caused by alcohol abuse and viral hepatitis, involve specific fibrogenic cell subpopulations.[95] Concerning the stroma reaction to hepatic tumors, we suggest that HSC-derived myofibroblasts and portal fibroblast-derived myofibroblasts are involved in the stroma reactions encountered in hepatocellular carcinomas and cholangiocarcinomas, respectively. Both types of cancer-associated myofibroblasts promote tumor progression.

Interestingly, scirrhous hepatocellular carcinoma, a rare variant of hepatocellular carcinoma, is characterized by abundant fibrous stroma and has been known to express several liver stem/progenitor cell markers.[269] It has been recently shown that scirrhous hepatocellular carcinomas harbor traits intermediate between hepatocellular carcinoma and cholangiocarcinoma including stem cell traits, which are similar to those of cholangiocarcinoma-like hepatocellular carcinoma.[270] It will be interesting to characterize the stromal cells involved in this particular hepatocellular carcinoma; we suggest that tumor cells

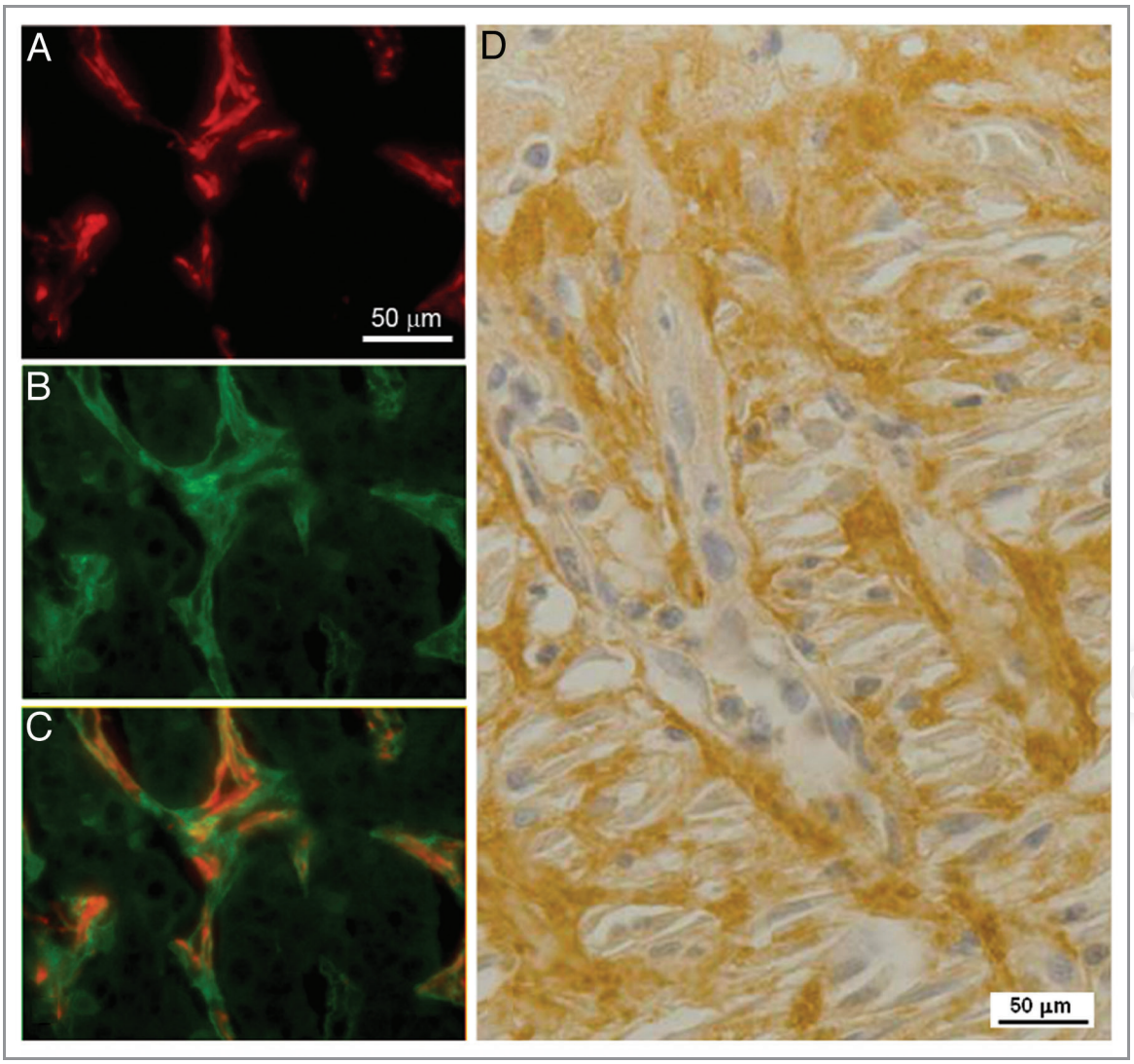


**Figure 4.** Expression of α-SMA and of periostin in the cholangiocarcinoma tissue and in rat granulation tissue. In the cholangiocarcinoma tissue, there is a strong staining for α-smooth muscle actin (α-SMA) in the stromal cells within the tumor (A). A similar distribution is seen with periostin staining (B). Merge image for the two proteins (C) shows that α-SMA and periostin are colocalized in stromal cells, though periostin (green) has a slightly wider distribution than α-SMA (red) as it is both intracellular in myofibroblasts and deposited in the matrix. (D) In the rat granulation tissue, a strong expression for periostin is observed in myofibroblasts, underlining the similarity between the stroma reaction and the granulation tissue.

derive from precursor cells able to acquire hepatocyte or cholangiocyte phenotype and located in Hering canals (see below) at the border between parenchyma and portal area.

The contribution of liver MSCs to the cancer-associated myofibroblast population is as yet unclear. Association of MSCs with the well characterized epithelial stem cells located in Hering canals, may constitute a niche and this concept is currently explored.[271] Several studies have demonstrated that, following injury, a significant proportion of myofibroblasts may originate from BM,[272] but the contribution of these cells to collagen production is not known.[273] Lineage tracing studies fail to demonstrate the generation of myofibroblasts from hepatic epithelial cells (hepatocytes and cholangiocytes) by EMT.[274] However, the controversy about the ability of hepatic epithelial cells to become myofibroblasts remains.[275] Thus, the possibility that MSCs, BM-derived cells and EMT represent alternative sources of cancer-associated myofibroblasts cannot be excluded at this time. Irrespectively, stroma-myofibroblast interactions represent an interesting tumor differentiation-independent target for therapy of cancers, particularly for hepatocellular carcinoma and cholangiocarcinoma.

Because of the lack of a good animal model, the pathogenesis of the stroma reaction in human hepatocellular carcinoma remains unclear. Different experimental models have been proposed to study hepatocellular carcinoma development. However, in most models, stroma reaction is practically absent. Using a model associating diethylnitrosamine exposure and N-nitrosomorpholine treatment, Taras and coworkers have observed that hepatocellular carcinoma cells were surrounded by a stroma reaction resembling that observed in humans.[276] In cholangiocarcinoma, models using

thioacetamide have been developed, mimicking correctly the multi-stage progression of human cholangiocarcinoma.[277,278] Finally, it is important to underline that the tumor stroma, beside representing a therapeutic target, is also a source of many potential new tumor biomarkers, and little is known regarding how changes in stromal gene expression affect cancer progression. Recently, the expression of stroma-related genes was analyzed in 122 hepatocellular carcinoma samples, and the results were related to patient prognosis;[279] the signature reveals the strong prognostic capacity of immune responses, angiogenic activity and ECM remodeling, highlighting the importance of stromal biology in hepatocellular carcinoma progression.

## Perspectives

Numerous studies have shown that the stroma regulates epithelial cell transformation, survival, cancer growth and metastasis.[232] Conversely, factors derived from the tumor activate local and circulating precursor cells in the stroma to generate this tumor-permissive microenvironment. It becomes increasingly clear that both tumor cells and stromal cells comprise tremendously heterogeneous cell populations. However, many activated stroma cells share myofibroblastic features irrespective of their origin. Functional cancer-associated myofibroblasts, i.e., ECM secreting and contracting stromal cells exhibiting α-SMA-positive stress fibers, play a central role in the detrimental cross-talk between tumor and stroma. Hence, anti-cancer strategies are conceivable with the aim to specifically target this phenotype in the tumor stroma. Such strategies can possibly target the contractile apparatus of the cancer-associated myofibroblast to reduce ECM stiffening,[280] which contributes to the persistence and progression of the tumor. Other approaches can include the inhibition of specific myofibroblast integrins that are important in cell mechanosensing and transmission of intracellular force to the ECM.[281]

Myofibroblast integrins are also possibly involved in activating the pro-tumorigenic factor TGFβ1. Due to its central role in acting on tumor and stroma cells, targeting TGFβ1 and TGFβ1 pathways is already clinically tested in therapeutic approaches.[170] Anti-TGFβ1 strategies include the use of small-molecule inhibitors of the TGFβ1 receptor type I kinase domain, TGFβ1-specific neutralizing antibodies and oligonucleotide antisense compounds.[170,282] Inhibiting the amplification loop operated by TGFβ1 on tumor cells leads to a decrease of tumor neovascularization and in the end to limit the tumor metastasis impairing with the dissemination of cells by the blood tract and acting directly on the cells. During this process it has been shown that Smad7 and I-Smad that inhibits TGFβ1 and bone morphogenetic protein signaling, efficiently inhibits lung and liver metastasis of mouse breast cancer JygMC(A) cells.[156] Smad7 also inhibited the migration and invasion of cells, indicating that Smad7 leads to prevention of the EMT process.[156] All these strategies principally aim in inhibiting later effects of the already active TGFβ1 during tumor formation and preventing metastasis of advanced cancers. However, intercepting already during the activation process of TGFβ1 mediated by a specific set of integrins emerges as alternative, possibly more targeted approach.[171,180,189] Another advantage of targeting integrins is that it will interfere with tumor development at multiple levels. Notably, anti-integrin strategies are already well developed to inhibit angiogenesis with the aim to cut off the cancer supply with oxygen and nutrients.[194]



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