

REVIEW

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Biomechanics of TGF β -induced epithelial-mesenchymal transition: implications for fibrosis and cancer

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Abstract

Fibrosis, a disease that results in loss of organ function, contributes to a significant number of deaths worldwide and sustained fibrotic activation has been suggested to increase the risk of developing cancer in a variety of tissues. Fibrogenesis and tumor progression are regulated in part through the activation and activity of myofibroblasts. Increasing evidence links myofibroblasts found within fibrotic lesions and the tumor microenvironment to a process termed epithelial-mesenchymal transition (EMT), a phenotypic change in which epithelial cells acquire mesenchymal characteristics. EMT can be stimulated by soluble signals, including transforming growth factor (TGF)- β , and recent studies have identified a role for mechanical cues in directing EMT. In this review, we describe the role that EMT plays in fibrogenesis and in the progression of cancer, with particular emphasis placed on biophysical signaling mechanisms that control the EMT program. We further describe specific TGF β -induced intracellular signaling cascades that are affected by cell- and tissue-level mechanics. Finally, we highlight the implications of mechanical induction of EMT on the development of treatments and targeted intervention strategies for fibrosis and cancer.

Keywords: Epithelial-mesenchymal transition; Biomechanics; Mechanotransduction; Myofibroblast; Fibrosis; Cancer; Transforming growth factor; Cell shape; Matrix rigidity

Introduction

Fibrotic diseases promote loss of function in a variety of organs including the heart, liver, lung, and kidney resulting in a significant number of deaths worldwide [1,2]. Fibrosis arises from deregulation of wound healing processes and is characterized by a stiff and collagen-rich extracellular matrix (ECM) that is resistant to degradation. Inappropriate activation and activity of myofibroblasts drives the development of fibrosis. An increased risk of developing cancer in a variety of tissues has been linked to high stromal collagen content and to the presence of fibrotic lesions [3-5]. Indeed, fibrosis has been found in close proximity of tumors within the pancreas [6], liver [7], and kidney [8] and myofibroblasts have been identified as residents of the tumor microenvironment [9,10]. The purpose of this article is to review the

role of myofibroblasts in fibrosis and cancer and to discuss how physical cues contribute to epithelial-mesenchymal transition and to the development of myofibroblasts.

Review

Myofibroblasts in health and disease

Myofibroblasts are specialized cells within the body that aid in wound healing. Upon activation by biochemical and mechanical signals, myofibroblasts secrete and organize ECM, develop specialized matrix adhesions [11], and exhibit cytoskeletal organization characterized by contractile actin filaments [12]. Together, these features allow for re-establishment of mechanical integrity and stability to the damaged tissue and enable the myofibroblasts to exert large contractile forces on their microenvironment thus assisting in both the closure of the wound and remodeling of the tissue [13,14]. When wound healing is complete, myofibroblasts undergo apoptosis which decreases the cellularity of the granulation tissue and promotes the formation of scar tissue [15]. Due to their important role in wound healing, these cells

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have attracted much interest for regenerative medicine applications.

Upon aberrant and chronic activation, myofibroblasts can mediate the development of fibrosis [16-20]. The sustained activation of myofibroblasts results in the enhanced production of ECM components, including collagen types I, III, IV, V, and VI and fibronectin [21-23]. Through integrin engagement with ECM components and cytoskeletal contractility, myofibroblasts exert large forces on the ECM thus enabling matrix assembly and alignment [24]. Together, these factors can lead to stiffening of the tissue and disruption of tissue architecture and function.

Studies suggest that myofibroblasts are key players in the progression of a variety of cancer types including lung [5], liver [3,25], breast [26], and gastric [27] cancer. Myofibroblasts have been found at the invasive fronts of tumors where they secrete pro-invasive cytokines, proteases, and inflammatory mediators [28-36]. Fibrotic lesions and myofibroblasts have also been found in the tumor microenvironment prior to cancer cell invasion into the stroma suggesting that myofibroblasts may mediate an invasive phenotype [37]. Indeed, myofibroblasts are found in higher proportions in the stroma of invasive breast cancers than in *in situ* carcinoma and their presence has been correlated with lymph node metastasis and increased histological grade in invasive ductal carcinoma [38,39]. Contrary to these reports, a recent study found that myofibroblasts may serve a protective role in the context of pancreatic cancer as depletion of myofibroblasts and fibrosis in a mouse model of pancreatic ductal adenocarcinoma leads to a more invasive cancer cell phenotype and reduced survival [40]. Depletion of myofibroblasts promoted remodeling of the pancreatic tumor stroma as well as changes in immune cell infiltration to the tumor. Thus, the effect of myofibroblasts on cancer progression appears to be complex and multifaceted and may vary depending upon organ or stage of cancer. Future investigation of the effect of *in vivo* myofibroblast depletion in other cancer types will be informative and will shed further light on the role of myofibroblasts in tumor progression.

Differentiation of myofibroblasts from fibroblasts

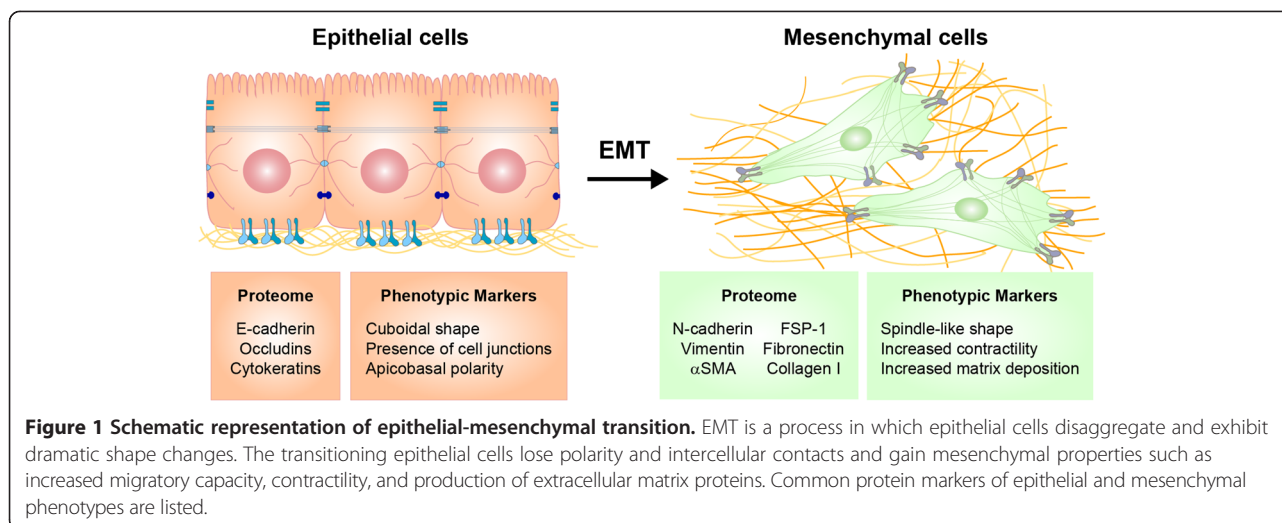
Following the identification of myofibroblasts, studies focused primarily on factors that regulate the differentiation of myofibroblasts from stromal fibroblasts. Transforming growth factor (TGF)- β is a potent inducer of the myofibroblast phenotype and TGF β -induced differentiation of fibroblasts to myofibroblasts was found to depend on the ED-A domain of fibronectin [41]. Hallmarks of differentiated myofibroblasts include *de novo* expression of alpha smooth muscle actin (α SMA) and the incorporation of α SMA into stress fibers which

confers high contractile activity to myofibroblasts. In this process, mechanical tension is crucial for the development of contractile features and for the acquisition of a myofibroblast phenotype [42-46]. Culture of fibroblasts on two-dimensional compliant substrata or within three-dimensional collagen gels has revealed that increased microenvironmental stiffness and tension results in increased differentiation of fibroblasts to myofibroblasts [43,47]. *In vitro* and *in vivo* experiments have also shown that changes in tensional loads to either collagen gels with embedded fibroblasts or granulation tissue at wound sites results in altered contractility of myofibroblasts [48,49]. Likewise, myofibroblasts can actively remodel both the chemical and physical properties of their microenvironment through the secretion of ECM and exertion of contractile forces [50]. Thus, mechanical signals are essential for the development of myofibroblasts from fibroblasts and for proper physiological function.

Epithelial cells mediate fibrogenesis

Epithelial-mesenchymal transition (EMT) is a form of epithelial plasticity that is important in normal embryonic development and is co-opted in the progression of pathological conditions including fibrosis and cancer [51-54]. In EMT, epithelial cells, which form monolayers that line many body structures and compartments, loosen attachments to neighboring cells, acquire an elongated morphology, and display increased motility (Figure 1). In addition to these phenotypic shifts, cells exhibit alterations in gene expression including upregulation of a variety of transcription factors including Snail, Slug, and Twist, decreased expression of epithelial markers such as E-cadherin and cytokeratins, and *de novo* expression of mesenchymal markers such as N-cadherin and vimentin [51,55]. Following early EMT marker changes, further progression through EMT can stimulate a myogenic program characterized by the expression of α SMA and a myofibroblast phenotype [56]. EMT is believed to contribute to fibrogenesis by serving as a source of myofibroblasts and by promoting paracrine signaling between epithelial cells and stromal cells. Several recent reviews highlight the role of EMT in epithelial-mesenchymal interactions in the context of fibrotic diseases [57-59].

Many studies have identified cells demonstrating features of EMT in fibrotic disease models and in human biopsy samples. In a model of liver fibrosis, hepatocytes upregulate the expression of the EMT-associated transcription factor Snail and hepatocyte-specific ablation of Snail protects mice from fibrotic progression [60]. In this study, it was found that hepatocyte expression of Snail has a multifaceted effect on the progression of liver fibrosis through regulation of growth factor expression and ECM synthesis, which impacts hepatocytes themselves and other cell types. Furthermore, hyperplastic type



II alveolar epithelial cells from patients suffering from idiopathic pulmonary fibrosis co-express epithelial and mesenchymal markers including α SMA [61-63]. In addition, human renal biopsy samples from patients with a variety of fibrotic kidney diseases display cells within the tubular structures that exhibit both epithelial and mesenchymal features [64,65]. Together, these findings lend strong support for an important role for the epithelium in fibrogenesis either as a precursor of myofibroblasts or as a mediator influencing the development of myofibroblasts from other cell types.

Given the importance of myofibroblasts in health and disease, much effort has been directed toward identification of myofibroblast progenitor cell types through lineage tracing studies in *in vivo* disease models. Studies have revealed a variety of candidates including resident fibroblasts, mesenchymal stem cells, and endothelial cells, with a number of reports finding that a portion of myofibroblasts within fibrotic lesions arise from epithelium through EMT [27,61,66-71]. Fate tracking of alveolar epithelial cells in genetically modified mice has demonstrated that mesenchymal cells arising during the progression of pulmonary fibrosis can originate from epithelial cells [61,69,70]. Moreover, lineage tracing in animal models has also identified epithelial cells as one of the cell types from which myofibroblasts can originate in kidney, liver, and intestinal fibrosis with the proportion of myofibroblasts arising from epithelial cells being tissue specific [66,71,72]. However, a series of recent fate mapping studies using different epithelial and mesenchymal tags showed no evidence of epithelial precursors to myofibroblasts in the kidney and liver suggesting an alternate precursor cell type or that the role of the epithelium in fibrogenesis may be organ or disease specific [64,73-77]. Thus, whether epithelial cells are indeed a source of myofibroblasts *in vivo* is currently debated and yet to be resolved definitively.

Several recent reviews provide a summary of the different viewpoints with regard to this debate [58,64,73].

Biochemical induction of EMT by TGF β

EMT is triggered by a variety of soluble factors including epidermal growth factor (EGF), hepatocyte growth factor (HGF), fibroblast growth factor (FGF), and TGF β [55,78-85]. Other stimuli, such as hypoxia [86,87] and adhesion to ECM components can also induce EMT [69,88,89]. TGF β , a ubiquitously expressed cytokine, is a potent inducer of EMT and is regarded as a key mediator of wound healing [90,91], fibrosis [92,93], and cancer [94,95]. Epithelial cells derived from a variety of tissues including lung [69,96,97], kidney [98-101], and breast [85,102-104] display myofibroblast features following exposure to TGF β . TGF β is perhaps the best characterized promoter of EMT and therefore we will focus this review specifically on TGF β -mediated EMT.

In the canonical TGF β signaling pathway, active TGF β ligands initiate signaling by binding to type I and type II receptor serine/threonine kinases. Following receptor activation, Smad2 and Smad3 associate with the TGF β receptor complex and are phosphorylated by the type I TGF β receptor. Phosphorylated Smad2 and Smad3 then form a complex with Smad4 and translocate to the nucleus. Once in the nucleus, the Smads can regulate the transcription of target genes in conjunction with other nuclear co-factors [105-107]. Activation of several Smad-independent pathways including phosphoinositide 3-kinase (PI3K)-Akt [108], focal adhesion kinase (FAK) [109], p38 mitogen-activated protein kinase (p38MAPK) [110], and extracellular signal-regulated kinase (Erk) [111] have been identified as crucial for EMT induction by TGF β and recent studies implicate hyaluronan synthase 2 (HAS2) [112], Krüppel-like factor (KLF)-8 [113], and microRNA miR-203 [114] as critical regulators of EMT.

During the progression of TGF β -induced EMT, cells exhibit dramatic cytoskeletal reorganization that is mediated by signaling through the Rho GTPase pathway which stimulates stress fiber formation, the acquisition of a mesenchymal morphology, and increased cytoskeletal contractility. Evidence implicates the RhoA pathway as a necessity for induction of EMT by TGF β [108,115]. These changes in cell morphology and cytoskeletal architecture suggest an important role for physical cues in regulating EMT.

Mechanical activation of TGF β

TGF β is synthesized by cells and stored in a latent form crosslinked to the ECM in the cellular microenvironment. TGF β can be activated via a number of mechanisms, one of which is through integrin binding. Integrin $\alpha_v\beta_6$, which is expressed at high levels predominantly on injured epithelial cells or cancer cells [116], binds to and locally activates TGF β *in vivo* and *in vitro* [117]. Treatment of lung epithelial cells with cytochalasin D, an inhibitor of actin polymerization, blocks activation of TGF β by $\alpha_v\beta_6$ demonstrating an important role for the actin cytoskeleton in inducing TGF β bioactivity [117]. A recent study suggests that cellular contractility is required for TGF β activation by $\alpha_v\beta_6$ as treatment of lung epithelial cells with Y27632 or blebbistatin, which inhibit Rho associated kinase (ROCK) and non-muscle myosin II respectively, abrogates TGF β activation [118]. Myofibroblasts can also activate TGF β through a combination of $\alpha_v\beta_5$ and $\alpha_v\beta_3$ integrin engagement and contractile forces *in vitro* [119]. Thus, cytoskeletal tension and cellular force generation are key mediators of the activation of TGF β signaling.

EMT alters the mechanical properties of cells

Cellular mechanics are influenced in part by the combination of cell morphology and cytoskeletal organization with the formation of stress fibers enabling increased cellular contractility [120]. Atomic force microscopy (AFM) is a useful tool to determine mechanical properties through gently applying a force to induce cell deformation from which the modulus of the cell can be determined. By employing AFM on kidney [121], alveolar [122], and mammary [123] epithelial cells, researchers have identified a significant increase in the stiffness of cells following TGF β treatment. Tension within the membrane, as determined by tether pulling experiments, was also found to increase after EMT induction [123]. In addition, the topography of cells changes following treatment with TGF β with a rougher surface profile [122] and nodular protrusions at intercellular junctions accompanying the transition to a mesenchymal phenotype [121]. These mechanical changes, in addition to cytoskeletal rearrangements, demonstrate a correlation

between cytoskeletal architecture and increased cell stiffness as epithelial cells progress through EMT. Furthermore, EMT has been observed at the edges of epithelial wounds [101,124] and AFM studies have found that cell stiffness peaks approximately 10-20 μm from the wound edge with lower localized mechanical stiffness at the wound edge and far from the wound edge within the intact epithelial monolayer [125]. This peak in mechanical stiffness was nullified with the expression of a dominant negative form of RhoA. These data suggest that wound sites may serve as focal points for mechanical signaling events and that changes in cellular stiffness may provide signals for cellular processes including cell spreading and migration which are required for the early stages of epithelial wound healing.

Increased cell spreading and elongation promote EMT

The shape of a cell is regulated by microenvironmental cues and has been shown to play a pivotal role in tissue morphogenesis [126,127], proliferation [128,129], apoptosis [128], and differentiation [130-133]. Cell shape is a consequence of intrinsic cellular mechanical properties and of forces exerted on the cell due to its adhesion to environmental components including ECM proteins and neighboring cells [134,135]. During EMT, cells experience drastic shape changes as they transition from a cuboidal, cobblestone morphology characteristic of epithelial cells to an elongated, spindle-like shape typical of mesenchymal cells.

Through the use of micropatterned cell culture substrata, which enable precise control over cell spreading, studies have shown that cell shape regulates the expression levels of the epithelial marker cytokeratin and the mesenchymal marker vimentin in matrix metalloproteinase (MMP)-3-induced EMT but not in TGF β -induced EMT [103]. More recently, we have demonstrated that cell spreading and elongation are critical factors that regulate TGF β -induced expression of the myofibroblast marker αSMA during EMT [104]. Culturing epithelial cells on microcontact printed islands of fibronectin of varying sizes and shapes enabled control of cell morphology. Adhesion to large square islands (2500 μm^2) which permitted cells to spread promoted an increase in the percentage of cells expressing αSMA after 48 hours of TGF β treatment in comparison to cells blocked from spreading (400 μm^2) and to control cells not treated with TGF β (Figure 2A). We found that cell shape regulates αSMA expression in part by controlling the subcellular localization of myocardin related transcription factor (MRTF)-A (Figure 2B). MRTFA is a co-factor of serum response factor (SRF) and together these proteins regulate the transcription of a variety of genes associated with actin dynamics and cell contractile function including αSMA [136,137]. Indeed, MRTFA plays a key role in TGF β -induced EMT [138] and contributes to

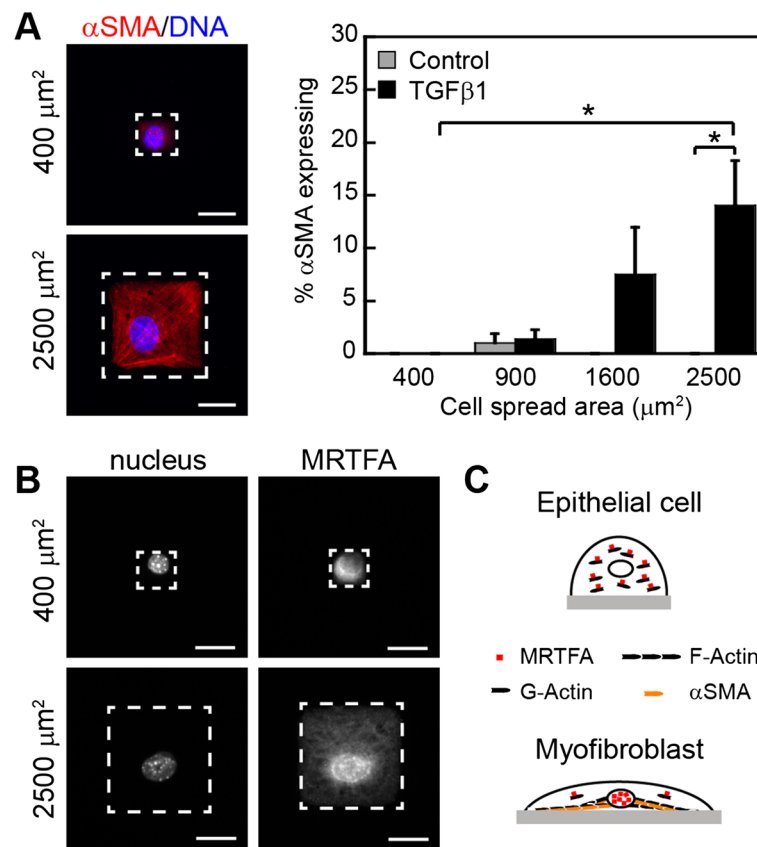


Figure 2 Cell shape regulates epithelial-myofibroblast transition. (A) Immunofluorescence staining and quantification of TGF β -induced α SMA expression for mouse mammary epithelial cells cultured on 400 μm^2 and 2500 μm^2 fibronectin islands. The percentage of cells expressing α SMA following a 48 hour treatment with TGF β or control vehicle was determined by immunofluorescence staining and microscopy. Cells with fluorescence intensities above background levels were scored as expressing α SMA. (B) Immunofluorescence staining for MRTFA in TGF β -treated NMuMG cells shows increased nuclear localization of MRTFA when cells are permitted to spread (2500 μm^2) in comparison to when cell spreading is blocked (400 μm^2). MRTFA localization was determined by comparing the mean nuclear and cytoplasmic fluorescence intensities within cells. Dashed lines represent the perimeter of the cell. Scale bars, 20 μm . Reported values are the mean of three independent experiments \pm standard error of the mean. * $p < 0.05$. (C) Proposed model demonstrating how cell spreading affects MRTFA subcellular localization and myofibroblast development. Adapted from O'Connor and Gomez, 2013 [104].

experimental fibrosis [139] and metastasis [140]. The activity of MRTFA is regulated in part by its association with monomeric (G)-actin and polymerization of actin monomers into filamentous (F)-actin disrupts the association between MRTFA and G-actin thus enabling nuclear accumulation of MRTFA [141]. Increased cell spreading promotes an increase in F-actin levels which then leads to MRTFA nuclear localization and transcriptional activity (Figure 2C). These data suggest that cell shape changes that accompany EMT are critical for induction of the myofibroblast phenotype.

Matrix rigidity controls EMT

Microenvironmental physical properties, such as stiffness and tension, are becoming increasingly acknowledged as contributing to normal cellular processes and to the development of diseases [142-145]. In wound healing, fibrosis, and cancer, epithelial cells exist in a

heterogeneous microenvironment in which the chemical and mechanical properties are dynamic. For example, during wound healing the mechanical properties at the wound site evolve with time, from compliant (with a Young's modulus of approximately 1 kPa) after initial wounding to a stiffness of 25 kPa or greater for contracting wound granulation tissue [146]. In fibrotic tissues, the elastic modulus can reach values as high as 15-100 kPa [147-150]. Interestingly, a recent study found that increased microenvironmental rigidity may precede liver fibrosis suggesting that the mechanical properties of the matrix may promote activation of pro-fibrotic pathways [143,151]. *In vivo* and *in vitro* studies have also linked increased tissue stiffness and collagen content to the tumor phenotype and metastasis [144,145,152]. For example, during the progression of breast cancer, the stiffness of the mammary gland can range from approximately 200 Pa for normal tissue to 5000 Pa or greater for the average breast

tumor [145,149,153]. High mammographic density, a strong risk factor for breast cancer [154,155], is associated with a significantly greater collagen content within the mammary gland in comparison to breast tissue with less mammographic density [4].

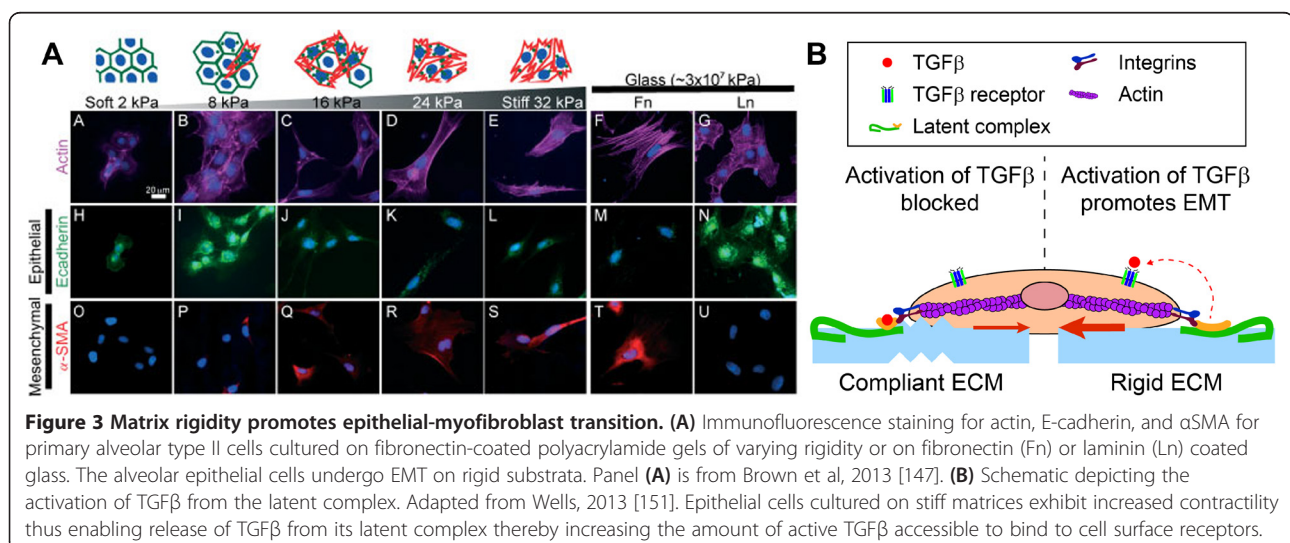
Recent studies have identified matrix rigidity as a crucial regulator of TGF β -induced EMT through several pathways [99,118,147,156]. Mammary and kidney epithelial cells exhibit a switch between TGF β -induced apoptosis and EMT when cultured on compliant or rigid substrata, respectively [99]. In these studies, soft substrata blocked and rigid substrata promoted EMT regardless of whether the cells were cultured on fibronectin, collagen I, or recombinant basement membrane. The switch between apoptosis and EMT is controlled by activation of the PI3K/Akt signaling pathway, with increasing matrix rigidity promoting increased phosphorylation of Akt. Furthermore, cells cultured on rigid matrices are able to generate contractile forces which promote TGF β activation from its latent complex by α_v integrins while compliant matrices block this process [118,119]. Activation of TGF β on rigid substrata is promoted by Rho/ROCK signaling in lung epithelial cells and this induces EMT (Figure 3) [118,147,156]. On fibronectin-coated substrata, this response can be abrogated by culturing cells on rigid substrata coated with a fibronectin mutant which contains a stabilized RGD and PHSRN synergy site that supports α_3 and α_5 integrin engagement [156]. These results highlight the complex interplay between epithelial cells and both the chemical and physical properties of their microenvironment during induction of EMT. Moreover, these studies suggest that activation of EMT may create a positive feedback loop that enhances myfibroblast activation and ECM

synthesis thereby further increasing the rigidity of the matrix and disease progression.

Tissue geometry patterns EMT

During tissue development and wound healing, cellular behaviors are spatially patterned thus conferring cells at specific locations unique attributes and functions. Indeed, patterning within developing embryos is ensured in part by the temporal and spatial regulation of EMT [52]. Moreover, myfibroblasts have been observed at the edges of epithelial wounds [101,124] and pathological EMT and myfibroblasts are found along the invasion front of metastatic tumors [95,157,158].

Spatial variations in the mechanical properties of tissues are controlled by tissue composition and architecture as well as by the interaction of individual cells with the surrounding matrix and neighboring cells. Within epithelial tissues, neighboring cells exhibit cell-cell adhesions that are mediated by tight junctions and adherens junctions. These cell-cell junctions are functionally and dynamically connected to the actin cytoskeleton thus enabling transmission of forces between neighboring cells. In culture, intercellular transmission of mechanical stress through cell-cell adhesions can establish mechanical gradients with regions of maximal stress defined by the geometry of the tissue [102,159]. Spatial patterns in EMT can arise in two-dimensional epithelial sheets with downregulation of cytokeratins and upregulation of mesenchymal markers vimentin and α SMA occurring in regions of the tissue that experience the highest mechanical stresses [102]. The observed spatial patterning of TGF β -induced EMT correlates with the subcellular localization of MRTFA, with EMT occurring in regions of the



tissues with the highest frequencies of MRTFA nuclear localization.

Cyclic stretch promotes EMT

Some cells within the body experience cyclic stretch during normal function, such as alveolar epithelia during respiration. Under conditions associated with fibrosis, epithelial cells may experience pathologically high levels of stretch arising from tissue distortion associated with injury or scar tissue formation. The effects of pathological levels of stretch on the induction of EMT have recently been highlighted in several studies. In a model system examining the pathological effects of renal tubular distension, kidney epithelial cells exposed to cyclic mechanical stretch exhibited increased EMT [160]. This effect was mediated by upregulation of TGF β by more than two-fold in stretched cells in comparison to non-stretched cells. Cyclic mechanical stretch also promotes EMT in type II alveolar epithelial cells, not through upregulation of TGF β , but rather by inducing actin polymerization and upregulation of low molecular weight hyaluronan which facilitates signaling through Wnt/ β -catenin and MyD88 pathways [161]. Together, these studies demonstrate yet another important way in which mechanical cues can promote EMT and the fibrotic response of tissues to injury.

Mechanosensitive signaling cascades in EMT

Myocardin related transcription factors

Acquisition of mesenchymal features during TGF β -induced EMT is regulated in part by the SRF/MRTFA signaling pathway and we have highlighted several studies demonstrating the interplay between this pathway and mechanics in EMT. Thus far, a majority of studies examining this pathway in the context of EMT have focused on how MRTFA regulates the expression of cytoskeletal-associated genes such as α SMA. MRTFA also regulates the expression of EMT-associated transcription factors including Snail, Slug, and Twist [105] and therefore may have an impact on the expression of the epithelial gene E-cadherin. Further studies are necessary to define the role of MRTFA in the regulation of epithelial markers during EMT and to determine the impact of mechanical cues on the loss of epithelial features during EMT.

Hippo pathway

The Hippo pathway is critical for cell growth and cell fate decisions and dysregulation of signaling through this pathway or of its downstream effectors is implicated in fibrosis and cancer [162-165]. Downstream effectors in this pathway, Yes-associated protein (YAP) and transcriptional co-activator with PDZ-binding motif (TAZ), interact with the canonical TGF β signaling cascade by regulating the subcellular localization of phosphorylated

Smads [166,167]. Activation of these factors is controlled in part by cell-cell contact [167] and recent studies have demonstrated that YAP and TAZ mediate how cells respond to cell geometry and ECM elasticity to control cell growth and stem cell differentiation [168-171]. Indeed, cell shape and matrix rigidity modulate the subcellular localization of YAP and TAZ and cytoskeletal destabilization and inhibition of cell contractility inactivate YAP and TAZ [168]. TAZ is a critical regulator of local EMT at wound sites [172] and overexpression of TAZ can induce EMT [173]. Downregulation of TAZ blocks α SMA expression along wound edges and it has been suggested that TAZ may control α SMA expression either through association with MRTFA or through interaction with the α SMA promoter as a co-activator to the TEA domain (TEAD) transcription factors [172]. Given that YAP and TAZ are mechanosensitive and cytoskeletal architecture is linked to Hippo pathway signaling [174], it is plausible that mechanical signals control YAP and TAZ activity to regulate aspects of EMT. Future studies addressing the interplay of mechanical cues and YAP and TAZ signal transduction during TGF β -induced EMT will be informative and may shed light on mechanisms mediating fibrosis and cancer.

Targeting TGF β -induced EMT

The multipotent nature of TGF β signaling in normal and diseased tissues presents challenges for the development of therapeutics targeting this pathway. Nevertheless, much effort has been directed toward the development of antagonists of TGF β [175-177]. Small molecule inhibitors are in various stages of development [177] and clinical trials are testing the efficacy of TGF β monoclonal antibodies for treatment of diabetic nephropathy and idiopathic pulmonary fibrosis [58]. Furthermore, neutralizing antibodies against TGF β have been found to reduce metastatic cancer progression in mice [178-182]. In addition, a promising approach which has demonstrated efficacy as an anti-fibrotic in lung, kidney, and liver disease models is targeting the integrin- and contractility-induced activation of TGF β from its latent complex through the use of a monoclonal antibody to $\alpha_v\beta_6$ integrin [183-186]. This method may also be an effective therapeutic approach for blocking tumor progression, as anti- $\alpha_v\beta_6$ integrin monoclonal antibody prevents xenograft tumor growth *in vivo* [187]. Inhibiting TGF β activation may present lower risk to the disruption of beneficial effects of TGF β than targeting TGF β itself since $\alpha_v\beta_6$ is expressed primarily within epithelial cells and is highly upregulated in diseased tissues [184].

Targeting intracellular signaling cascades downstream of TGF β rather than TGF β itself may also be a viable approach for blocking fibrogenesis and cancer progression. Indeed, a recent study demonstrated that troglitazone, a peroxisome proliferator activated receptor (PPAR)- γ

agonist that suppresses TGF β -mediated fibrogenesis [188-190], attenuates TGF β -induced phosphorylation of Akt and upregulation of Snail [97]. This is one of the major pathways activated within epithelial cells by the combination of TGF β and matrix rigidity [99]. In addition, small molecule inhibitors including CCG-1423 and its analogs block SRF/MRTFA signaling [191,192]. Namely, CCG-1423 blocks the interaction of MRTFA with importin alpha/beta 1 thus preventing the nuclear import of MRTFA [193]. Furthermore, CCG-1423 has been shown to successfully inhibit TGF β -induced expression of α SMA [102,104,194]. Interestingly, a recent study reported that the small molecule isoxazole can induce a myofibroblast phenotype by regulating the stability and activity of MRTFA [195]. Isoxazole enhanced cutaneous wound closure in mice suggesting that therapeutics aimed at promoting MRTFA signaling and the myofibroblast phenotype may also be promising methods for improving wound healing.

Given the link between TGF β -induced EMT, fibrosis, and cancer, therapeutics directly targeting EMT may prove to be fruitful approaches for treating these diseases. Bone morphogenetic protein (BMP)-7 exhibits anti-fibrotic effects in animal models of renal fibrosis and reverses EMT in renal tubular cells *in vitro* [100,196]. Furthermore, a recent study found that a variety of anti-proliferative agents also inhibit EMT suggesting that the most effective compounds for cancer treatment may be those that target multiple aspects of cancer progression [197].

Conclusions

The ability of epithelial cells to transition to a mesenchymal phenotype is regulated by cytokines, ECM components, cell-cell contacts, and mechanical cues and a combination of these factors is likely required for EMT induction. The studies highlighted within this review have identified an important role for mechanics in TGF β -induced EMT and suggest that mechanical signaling pathways, including those involved in mechanotransduction, cell contractility, and regulation of matrix rigidity, could serve as potential targets for new therapies directed toward fibrosis and cancer. To achieve this though, a better understanding of the mechanistic underpinnings of how cell and tissue level physical properties contribute to EMT in pathological settings is needed.

Abbreviations

AFM: Atomic force microscopy; BMP: Bone morphogenetic protein; ECM: Extracellular matrix; EGF: Epidermal growth factor; EMT: Epithelial-mesenchymal transition; FAK: Focal adhesion kinase; FGF: Fibroblast growth factor; Fn: Fibronectin; FSP-1: Fibroblast-specific protein-1; HAS2: Hyaluronan synthase 2; HGF: Hepatocyte growth factor; KLF8: Krüppel-like factor 8; Ln: Laminin; MAPK: Mitogen-activated protein kinase; MMP: Matrix metalloproteinase; MRTF: Myocardin related transcription factor; NMuMG: Normal murine mammary gland; PI3K: Phosphoinositide-3-kinase;

PPAR: Peroxisome proliferator activated receptor; ROCK: Rho associated kinase; SRF: Serum response factor; TAZ: Transcriptional co-activator with PDZ-binding motif; TEAD: TEA domain; TGF: Transforming growth factor; YAP: Yes-associated protein; α SMA: Alpha smooth muscle actin.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

JWO and EWG reviewed the literature, wrote, and revised the manuscript. Both authors read and approved the final manuscript.

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References

1. Zeisberg M, Kalluri R: Cellular mechanisms of tissue fibrosis. 1: common and organ-specific mechanisms associated with tissue fibrosis. *Am J Physiol Cell Physiol* 2013, **304**:C216–C225.
2. Wynn TA: Cellular and molecular mechanisms of fibrosis. *J Pathol* 2008, **214**:199–210.
3. Bissell DM: Chronic liver injury, TGF-beta, and cancer. *Exp Mol Med* 2001, **33**:179–190.
4. Boyd NF, Rommens JM, Vogt K, Lee V, Hopper JL, Yaffe MJ, Paterson AD: Mammographic breast density as an intermediate phenotype for breast cancer. *Lancet Oncol* 2005, **6**:798–808.
5. Daniels CE, Jett JR: Does interstitial lung disease predispose to lung cancer? *Curr Opin Pulm Med* 2005, **11**:431–437.
6. Shields MA, Dangi-Garimella S, Redig AJ, Munshi HG: Biochemical role of the collagen-rich tumour microenvironment in pancreatic cancer progression. *Biochem J* 2012, **441**:541–552.
7. Zhang DY, Friedman SL: Fibrosis-dependent mechanisms of hepatocarcinogenesis. *Hepatology* 2012, **56**:769–775.
8. Lopez-Novoa JM, Nieto MA: Inflammation and EMT: an alliance towards organ fibrosis and cancer progression. *EMBO Mol Med* 2009, **1**:303–314.
9. Bhowmick NA, Neilson EG, Moses HL: Stromal fibroblasts in cancer initiation and progression. *Nature* 2004, **432**:332–337.
10. Elenbaas B, Weinberg RA: Heterotypic signaling between epithelial tumor cells and fibroblasts in carcinoma formation. *Exp Cell Res* 2001, **264**:169–184.
11. Hinz B, Dugina V, Ballestrem C, Wehrle-Haller B, Chaponnier C: Alpha-smooth muscle actin is crucial for focal adhesion maturation in myofibroblasts. *Mol Biol Cell* 2003, **14**:2508–2519.
12. Gabbiani G, Ryan GB, Majne G: Presence of modified fibroblasts in granulation tissue and their possible role in wound contraction. *Experientia* 1971, **27**:549–550.
13. Tomasek JJ, Gabbiani G, Hinz B, Chaponnier C, Brown RA: Myofibroblasts and mechano-regulation of connective tissue remodelling. *Nat Rev Mol Cell Biol* 2002, **3**:349–363.
14. Hinz B: Formation and function of the myofibroblast during tissue repair. *J Invest Dermatol* 2007, **127**:526–537.
15. Desmouliere A, Redard M, Darby I, Gabbiani G: Apoptosis mediates the decrease in cellularity during the transition between granulation tissue and scar. *Am J Pathol* 1995, **146**:56–66.
16. Brown RD, Ambler SK, Mitchell MD, Long CS: The cardiac fibroblast: therapeutic target in myocardial remodeling and failure. *Annu Rev Pharmacol Toxicol* 2005, **45**:657–687.
17. Gressner AM, Weiskirchen R: Modern pathogenetic concepts of liver fibrosis suggest stellate cells and TGF-beta as major players and therapeutic targets. *J Cell Mol Med* 2006, **10**:76–99.
18. Liu Y: Renal fibrosis: new insights into the pathogenesis and therapeutics. *Kidney Int* 2006, **69**:213–217.
19. Phan SH: The myofibroblast in pulmonary fibrosis. *Chest* 2002, **122**:286S–289S.
20. Thannickal VJ, Toews GB, White ES, Lynch JP III, Martinez FJ: Mechanisms of pulmonary fibrosis. *Annu Rev Med* 2004, **55**:395–417.

21. Klingberg F, Hinz B, White ES: **The myofibroblast matrix: implications for tissue repair and fibrosis.** *J Pathol* 2013, **229**:298–309.
22. Zhang K, Rekhter MD, Gordon D, Phan SH: **Myofibroblasts and their role in lung collagen gene expression during pulmonary fibrosis: a combined immunohistochemical and in situ hybridization study.** *Am J Pathol* 1994, **145**:114–125.
23. Balza E, Borsi L, Allemanni G, Zardi L: **Transforming growth factor beta regulates the levels of different fibronectin isoforms in normal human cultured fibroblasts.** *FEBS Lett* 1988, **228**:42–44.
24. Zhong C, Chrzanowska-Wodnicka M, Brown J, Shaub A, Belkin AM, Burrigide K: **Rho-mediated contractility exposes a cryptic site in fibronectin and induces fibronectin matrix assembly.** *J Cell Biol* 1998, **141**:539–551.
25. Neaud V, Faouzi S, Guirouilh J, Le Bail B, Balabaud C, Bioulac-Sage P, Rosenbaum J: **Human hepatic myofibroblasts increase invasiveness of hepatocellular carcinoma cells: evidence for a role of hepatocyte growth factor.** *Hepatology* 1997, **26**:1458–1466.
26. Radisky DC, Kenny PA, Bissell MJ: **Fibrosis and cancer: do myofibroblasts come also from epithelial cells via EMT?** *J Cell Biochem* 2007, **101**:830–839.
27. Quante M, Tu SP, Tomita H, Gonda T, Wang SS, Takashi S, Baik GH, Shibata W, Diprete B, Betz KS, Friedman R, Varro A, Tycko B, Wang TC: **Bone marrow-derived myofibroblasts contribute to the mesenchymal stem cell niche and promote tumor growth.** *Cancer Cell* 2011, **19**:257–272.
28. Nielsen BS, Sehested M, Timshel S, Pyke C, Dano K: **Messenger RNA for urokinase plasminogen activator is expressed in myofibroblasts adjacent to cancer cells in human breast cancer.** *Lab Invest* 1996, **74**:168–177.
29. Ronnov-Jessen L, Petersen OW, Kotliansky VE, Bissell MJ: **The origin of the myofibroblasts in breast cancer: recapitulation of tumor environment in culture unravels diversity and implicates converted fibroblasts and recruited smooth muscle cells.** *J Clin Invest* 1995, **95**:859–873.
30. Bisson C, Blacher S, Polette M, Blanc JF, Kebers F, Desreux J, Tetu B, Rosenbaum J, Foidart JM, Birembaut P, Noel A: **Restricted expression of membrane type 1-matrix metalloproteinase by myofibroblasts adjacent to human breast cancer cells.** *Int J Cancer* 2003, **105**:7–13.
31. Offersen BV, Nielsen BS, Hoyer-Hansen G, Rank F, Hamilton-Dutoit S, Overgaard J, Andreasen PA: **The myofibroblast is the predominant plasminogen activator inhibitor-1-expressing cell type in human breast carcinomas.** *Am J Pathol* 2003, **163**:1887–1899.
32. Nielsen BS, Rank F, Lopez JM, Balbin M, Vizoso F, Lund LR, Dano K, Lopez-Otin C: **Collagenase-3 expression in breast myofibroblasts as a molecular marker of transition of ductal carcinoma in situ lesions to invasive ductal carcinomas.** *Cancer Res* 2001, **61**:7091–7100.
33. Sivridis E, Giatromanolaki A, Koukourakis MI: **Proliferating fibroblasts at the invading tumour edge of colorectal adenocarcinomas are associated with endogenous markers of hypoxia, acidity, and oxidative stress.** *J Clin Pathol* 2005, **58**:1033–1038.
34. Ohtani H, Motohashi H, Sato H, Seiki M, Nagura H: **Dual over-expression pattern of membrane-type metalloproteinase-1 in cancer and stromal cells in human gastrointestinal carcinoma revealed by in situ hybridization and immunoelectron microscopy.** *Int J Cancer* 1996, **68**:565–570.
35. Gress TM, Muller-Pillasch F, Lerch MM, Friess H, Buchler M, Adler G: **Expression and in-situ localization of genes coding for extracellular matrix proteins and extracellular matrix degrading proteases in pancreatic cancer.** *Int J Cancer* 1995, **62**:407–413.
36. Vermeulen L, De Sousa EMF, van der Heijden M, Cameron K, de Jong JH, Borovski T, Tuijnman JB, Todaro M, Merz C, Rodermond H, Sprick MR, Kemper K, Richel DJ, Stassi G, Medema JP: **Wnt activity defines colon cancer stem cells and is regulated by the microenvironment.** *Nat Cell Biol* 2010, **12**:468–476.
37. De Wever O, Mareel M: **Role of tissue stroma in cancer cell invasion.** *J Pathol* 2003, **200**:429–447.
38. Yazhou C, Wenlv S, Weidong Z, Licun W: **Clinicopathological significance of stromal myofibroblasts in invasive ductal carcinoma of the breast.** *Tumour Biol* 2004, **25**:290–295.
39. De Wever O, Mareel M: **Role of myofibroblasts at the invasion front.** *Biol Chem* 2002, **383**:55–67.
40. Ozdemir BC, Pentcheva-Hoang T, Carstens JL, Zheng X, Wu CC, Simpson TR, Laklai H, Sugimoto H, Kahlert C, Novitskiy SV, De Jesus-Acosta A, Sharma P, Heidari P, Mahmood U, Chin L, Moses HL, Weaver VM, Maitra A, Allison JP, LeBleu VS, Kalluri R: **Depletion of carcinoma-associated fibroblasts and fibrosis induces immunosuppression and accelerates pancreas cancer with reduced survival.** *Cancer Cell* 2014, **25**:719–734.
41. Serini G, Bochaton-Piallat ML, Ropraz P, Geinoz A, Borsi L, Zardi L, Gabbiani G: **The fibronectin domain ED-A is crucial for myofibroblastic phenotype induction by transforming growth factor-beta 1.** *J Cell Biol* 1998, **142**:873–881.
42. Arora PD, Narani N, McCulloch CA: **The compliance of collagen gels regulates transforming growth factor-beta induction of alpha-smooth muscle actin in fibroblasts.** *Am J Pathol* 1999, **154**:871–882.
43. Grinnell F, Ho CH, Lin YC, Skuta G: **Differences in the regulation of fibroblast contraction of floating versus stressed collagen matrices.** *J Biol Chem* 1999, **274**:918–923.
44. Grinnell F, Zhu M, Carlson MA, Abrams JM: **Release of mechanical tension triggers apoptosis of human fibroblasts in a model of regressing granulation tissue.** *Exp Cell Res* 1999, **248**:608–619.
45. Squier CA: **The effect of stretching on formation of myofibroblasts in mouse skin.** *Cell Tissue Res* 1981, **220**:325–335.
46. Tomasek JJ, Haaksma CJ, Eddy RJ, Vaughan MB: **Fibroblast contraction occurs on release of tension in attached collagen lattices: dependency on an organized actin cytoskeleton and serum.** *Anat Rec* 1992, **232**:359–368.
47. Li Z, Dranoff JA, Chan EP, Uemura M, Sevigny J, Wells RG: **Transforming growth factor-beta and substrate stiffness regulate portal fibroblast activation in culture.** *Hepatology* 2007, **46**:1246–1256.
48. Brown RA, Prajapati R, McGrouther DA, Yannas IV, Eastwood M: **Tensional homeostasis in dermal fibroblasts: mechanical responses to mechanical loading in three-dimensional substrates.** *J Cell Physiol* 1998, **175**:323–332.
49. Hinz B, Mastrangelo D, Iselin CE, Chaponnier C, Gabbiani G: **Mechanical tension controls granulation tissue contractile activity and myofibroblast differentiation.** *Am J Pathol* 2001, **159**:1009–1020.
50. Leung LY, Tian D, Brangwynne CP, Weitz DA, Tschumperlin DJ: **A new microrheometric approach reveals individual and cooperative roles for TGF-beta1 and IL-1beta in fibroblast-mediated stiffening of collagen gels.** *FASEB J* 2007, **21**:2064–2073.
51. Kalluri R, Weinberg RA: **The basics of epithelial-mesenchymal transition.** *J Clin Invest* 2009, **119**:1420–1428.
52. Shook D, Keller R: **Mechanisms, mechanics and function of epithelial-mesenchymal transitions in early development.** *Mech Dev* 2003, **120**:1351–1383.
53. Thiery JP, Acloque H, Huang RY, Nieto MA: **Epithelial-mesenchymal transitions in development and disease.** *Cell* 2009, **139**:871–890.
54. Xu J, Lamouille S, Derynck R: **TGF-beta-induced epithelial to mesenchymal transition.** *Cell Res* 2009, **19**:156–172.
55. Lamouille S, Xu J, Derynck R: **Molecular mechanisms of epithelial-mesenchymal transition.** *Nat Rev Mol Cell Biol* 2014, **15**:178–196.
56. Masszi A, Speight P, Charbonney E, Lodyga M, Nakano H, Szasz K, Kapus A: **Fate-determining mechanisms in epithelial-myofibroblast transition: major inhibitory role for Smad3.** *J Cell Biol* 2010, **188**:383–399.
57. Chapman HA: **Epithelial-mesenchymal interactions in pulmonary fibrosis.** *Annu Rev Physiol* 2011, **73**:413–435.
58. Duffield JS, Lupher M, Thannickal VJ, Wynn TA: **Host responses in tissue repair and fibrosis.** *Annu Rev Pathol* 2013, **8**:241–276.
59. Friedman SL, Sheppard D, Duffield JS, Violette S: **Therapy for fibrotic diseases: nearing the starting line.** *Sci Transl Med* 2013, **5**:167sr161.
60. Rowe RG, Lin Y, Shimizu-Hirota R, Hanada S, Neilson EG, Greenson JK, Weiss SJ: **Hepatocyte-derived Snail1 propagates liver fibrosis progression.** *Mol Cell Biol* 2011, **31**:2392–2403.
61. Kim KK, Kugler MC, Wolters PJ, Robillard L, Galvez MG, Brumwell AN, Sheppard D, Chapman HA: **Alveolar epithelial cell mesenchymal transition develops in vivo during pulmonary fibrosis and is regulated by the extracellular matrix.** *Proc Natl Acad Sci U S A* 2006, **103**:13180–13185.
62. Willis BC, Borok Z: **TGF-beta-induced EMT: mechanisms and implications for fibrotic lung disease.** *Am J Physiol Lung Cell Mol Physiol* 2007, **293**:L525–L534.
63. Marmai C, Sutherland RE, Kim KK, Dolganov GM, Fang X, Kim SS, Jiang S, Golden JA, Hoopes CW, Matthay MA, Chapman HA, Wolters PJ: **Alveolar epithelial cells express mesenchymal proteins in patients with idiopathic pulmonary fibrosis.** *Am J Physiol Lung Cell Mol Physiol* 2011, **301**:L71–L78.
64. Quaggin SE, Kapus A: **Scar wars: mapping the fate of epithelial-mesenchymal-myofibroblast transition.** *Kidney Int* 2011, **80**:41–50.

65. Rastaldi MP, Ferrario F, Giardino L, Dell'Antonio G, Grillo C, Grillo P, Strutz F, Muller GA, Colasanti G, D'Amico G: **Epithelial-mesenchymal transition of tubular epithelial cells in human renal biopsies.** *Kidney Int* 2002, **62**:137–146.
66. Flier SN, Tanjore H, Kokkotou EG, Sugimoto H, Zeisberg M, Kalluri R: **Identification of epithelial to mesenchymal transition as a novel source of fibroblasts in intestinal fibrosis.** *J Biol Chem* 2010, **285**:20202–20212.
67. Hinz B, Phan SH, Thannickal VJ, Galli A, Bochaton-Piallat ML, Gabbiani G: **The myofibroblast: one function, multiple origins.** *Am J Pathol* 2007, **170**:1807–1816.
68. Iwano M, Plieth D, Danoff TM, Xue C, Okada H, Neilson EG: **Evidence that fibroblasts derive from epithelium during tissue fibrosis.** *J Clin Invest* 2002, **110**:341–350.
69. Kim KK, Wei Y, Szekeres C, Kugler MC, Wolters PJ, Hill ML, Frank JA, Brumwell AN, Wheeler SE, Kreidberg JA, Chapman HA: **Epithelial cell alpha3beta1 integrin links beta-catenin and Smad signaling to promote myofibroblast formation and pulmonary fibrosis.** *J Clin Invest* 2009, **119**:213–224.
70. Tanjore H, Xu XC, Polosukhin W, Degryse AL, Li B, Han W, Sherrill TP, Plieth D, Neilson EG, Blackwell TS, Lawson WE: **Contribution of epithelial-derived fibroblasts to bleomycin-induced lung fibrosis.** *Am J Respir Crit Care Med* 2009, **180**:657–665.
71. Zeisberg M, Yang C, Martino M, Duncan MB, Rieder F, Tanjore H, Kalluri R: **Fibroblasts derive from hepatocytes in liver fibrosis via epithelial to mesenchymal transition.** *J Biol Chem* 2007, **282**:23337–23347.
72. LeBleu VS, Taduri G, O'Connell J, Teng Y, Cooke VG, Woda C, Sugimoto H, Kalluri R: **Origin and function of myofibroblasts in kidney fibrosis.** *Nat Med* 2013, **19**:1047–1053.
73. Zeisberg M, Duffield JS: **Resolved: EMT produces fibroblasts in the kidney.** *J Am Soc Nephrol* 2010, **21**:1247–1253.
74. Humphreys BD, Lin SL, Kobayashi A, Hudson TE, Nowlin BT, Bonventre JV, Valerius MT, McMahon AP, Duffield JS: **Fate tracing reveals the pericyte and not epithelial origin of myofibroblasts in kidney fibrosis.** *Am J Pathol* 2010, **176**:85–97.
75. Koesters R, Kaissling B, Lehir M, Picard N, Theilig F, Gebhardt R, Glick AB, Hahnel B, Hosser H, Grone HJ, Kriz W: **Tubular overexpression of transforming growth factor-beta1 induces autophagy and fibrosis but not mesenchymal transition of renal epithelial cells.** *Am J Pathol* 2010, **177**:632–643.
76. Taura K, Miura K, Iwaisako K, Osterreicher CH, Kodama Y, Penz-Osterreicher M, Brenner DA: **Hepatocytes do not undergo epithelial-mesenchymal transition in liver fibrosis in mice.** *Hepatology* 2010, **51**:1027–1036.
77. Scholten D, Osterreicher CH, Scholten A, Iwaisako K, Gu G, Brenner DA, Kisseleva T: **Genetic labeling does not detect epithelial-to-mesenchymal transition of cholangiocytes in liver fibrosis in mice.** *Gastroenterology* 2010, **139**:987–998.
78. Lo H-W, Hsu S-C, Xia W, Cao X, Shih J-Y, Wei Y, Abbruzzese JL, Hortobagyi GN, Hung M-C: **Epidermal growth factor receptor cooperates with signal transducer and activator of transcription 3 to induce epithelial-mesenchymal transition in cancer cells via up-regulation of TWIST gene expression.** *Cancer Res* 2007, **67**:9066–9076.
79. Lu ZM, Ghosh S, Wang ZY, Hunter T: **Downregulation of caveolin-1 function by EGF leads to the loss of E-cadherin, increased transcriptional activity of beta-catenin, and enhanced tumor cell invasion.** *Cancer Cell* 2003, **4**:499–515.
80. Elliott BE, Hung WL, Boag AH, Tuck AB: **The role of hepatocyte growth factor (scatter factor) in epithelial-mesenchymal transition and breast cancer.** *Can J Physiol Pharm* 2002, **80**:91–102.
81. Grotegut S, von Schweinitz D, Christofori G, Lehembre F: **Hepatocyte growth factor induces cell scattering through MAPK/Egr-1-mediated upregulation of Snail.** *EMBO J* 2006, **25**:3534–3545.
82. Valles AM, Boyer B, Badet J, Tucker GC, Barritault D, Thiery JP: **Acidic Fibroblast growth-factor is a modulator of epithelial plasticity in a rat bladder-carcinoma cell-line.** *Proc Natl Acad Sci U S A* 1990, **87**:1124–1128.
83. Ciruna B, Rossant J: **FGF signaling regulates mesoderm cell fate specification and morphogenetic movement at the primitive streak.** *Dev Cell* 2001, **1**:37–49.
84. Miettinen PJ, Ebner R, Lopez AR, Derynck R: **TGF-beta induced transdifferentiation of mammary epithelial cells to mesenchymal cells - involvement of type-I receptors.** *J Cell Biol* 1994, **127**:2021–2036.
85. Xie L, Law BK, Aakre ME, Edgerton M, Shyr Y, Bhowmick NA, Moses HL: **Transforming growth factor beta-regulated gene expression in a mouse mammary gland epithelial cell line.** *Breast Cancer Res* 2003, **5**:R187–R198.
86. Sahlgren C, Gustafsson MV, Jin S, Poellinger L, Lendahl U: **Notch signaling mediates hypoxia-induced tumor cell migration and invasion.** *Proc Natl Acad Sci U S A* 2008, **105**:6392–6397.
87. Higgins DF, Kimura K, Bernhardt WM, Shrimanker N, Akai Y, Hohenstein B, Saito Y, Johnson RS, Kretzler M, Cohen CD, Eckardt K-U, Iwano M, Haase VH: **Hypoxia promotes fibrogenesis in vivo via HIF-1 stimulation of epithelial-to-mesenchymal transition.** *J Clin Invest* 2007, **117**:3810–3820.
88. Espinosa Neira R, Perez Salazar E: **Native type IV collagen induces an epithelial to mesenchymal transition-like process in mammary epithelial cells MCF10A.** *Int J Biochem Cell B* 2012, **44**:2194–2203.
89. Zeisberg M, Bonner G, Maeshima Y, Colorado P, Muller GA, Strutz F, Kalluri R: **Renal fibrosis: collagen composition and assembly regulates epithelial-mesenchymal transdifferentiation.** *Am J Pathol* 2001, **159**:1313–1321.
90. Klass BR, Grobbelaar AO, Rolfe KJ: **Transforming growth factor beta 1 signalling, wound healing and repair: a multifunctional cytokine with clinical implications for wound repair, a delicate balance.** *Postgrad Med J* 2009, **85**:9–14.
91. Levine JH, Moses HL, Gold LI, Nanney LB: **Spatial and temporal patterns of immunoreactive transforming growth factor-beta-1, beta-2, beta-3 during excisional wound repair.** *Am J Pathol* 1993, **143**:368–380.
92. Ask K, Bonniaud P, Maass K, Eickelberg O, Margetts PJ, Warburton D, Groffen J, Gauldie J, Kolb M: **Progressive pulmonary fibrosis is mediated by TGF-beta isoform 1 but not TGF-beta 3.** *Int J Biochem Cell B* 2008, **40**:484–495.
93. Bottinger EP: **TGF-beta in renal injury and disease.** *Semin Nephrol* 2007, **27**:309–320.
94. Gorsch SM, Memoli VA, Stukel TA, Gold LI, Arrick BA: **Immunohistochemical staining for transforming growth factor-beta-1 associates with disease progression in human breast cancer.** *Cancer Res* 1992, **52**:6949–6952.
95. Oft M, Heider KH, Beug H: **TGFbeta signaling is necessary for carcinoma cell invasiveness and metastasis.** *Curr Biol* 1998, **8**:1243–1252.
96. Willis BC, Liebler JM, Luby-Phelps K, Nicholson AG, Crandall ED, du Bois RM, Borok Z: **Induction of epithelial-mesenchymal transition in alveolar epithelial cells by transforming growth factor-beta1: potential role in idiopathic pulmonary fibrosis.** *Am J Pathol* 2005, **166**:1321–1332.
97. Zhou B, Buckley ST, Patel V, Liu Y, Luo J, Krishnaveni MS, Ivan M, DeMaio L, Kim KJ, Ehrhardt C, Crandall ED, Borok Z: **Troglitazone attenuates TGF-beta1-induced EMT in alveolar epithelial cells via a PPARgamma-independent mechanism.** *PLoS One* 2012, **7**:e38827.
98. Elberg G, Chen L, Elberg D, Chan MD, Logan CJ, Turman MA: **MKL1 mediates TGF-beta1-induced alpha-smooth muscle actin expression in human renal epithelial cells.** *Am J Physiol Renal Physiol* 2008, **294**:F1116–F1128.
99. Leight JL, Wozniak MA, Chen S, Lynch ML, Chen CS: **Matrix rigidity regulates a switch between TGF-beta 1-induced apoptosis and epithelial-mesenchymal transition.** *Mol Biol Cell* 2012, **23**:781–791.
100. Zeisberg M, Hanai J, Sugimoto H, Mammoto T, Charytan D, Strutz F, Kalluri R: **BMP-7 counteracts TGF-beta1-induced epithelial-to-mesenchymal transition and reverses chronic renal injury.** *Nat Med* 2003, **9**:964–968.
101. Masszi A, Fan L, Rosivall L, McCulloch CA, Rotstein OD, Mucci I, Kapus A: **Integrity of cell-cell contacts is a critical regulator of TGF-beta 1-induced epithelial-to-myofibroblast transition: role for beta-catenin.** *Am J Pathol* 2004, **165**:1955–1967.
102. Gomez EW, Chen QK, Gjorevski N, Nelson CM: **Tissue geometry patterns epithelial-mesenchymal transition via intercellular mechanotransduction.** *J Cell Biochem* 2010, **110**:44–51.
103. Nelson CM, Khaou D, Bissell MJ, Radisky DC: **Change in cell shape is required for matrix metalloproteinase-induced epithelial-mesenchymal transition of mammary epithelial cells.** *J Cell Biochem* 2008, **105**:25–33.
104. O'Connor JW, Gomez EW: **Cell adhesion and shape regulate TGF-beta1-induced epithelial-myofibroblast transition via MRTF-A signalling.** *PLoS One* 2013, **8**:e83188.
105. Morita T, Mayanagi T, Sobue K: **Dual roles of myocardin-related transcription factors in epithelial mesenchymal transition via slug induction and actin remodeling.** *J Cell Biol* 2007, **179**:1027–1042.

106. Shi YG, Massague J: **Mechanisms of TGF-beta signaling from cell membrane to the nucleus.** *Cell* 2003, **113**:685–700.
107. Zavadil J, Bitzer M, Liang D, Yang YC, Massimi A, Kneitz S, Piek E, Bottinger EP: **Genetic programs of epithelial cell plasticity directed by transforming growth factor-beta.** *Proc Natl Acad Sci U S A* 2001, **98**:6686–6691.
108. Bakin AV, Tomlinson AK, Bhowmick NA, Moses HL, Arteaga CL: **Phosphatidylinositol 3-kinase function is required for transforming growth factor beta-mediated epithelial to mesenchymal transition and cell migration.** *J Biol Chem* 2000, **275**:36803–36810.
109. Cicchini C, Laudadio I, Citarella F, Corazzari M, Steindler C, Conigliaro A, Fantoni A, Amicone L, Tripodi M: **TGFbeta-induced EMT requires focal adhesion kinase (FAK) signaling.** *Exp Cell Res* 2008, **314**:143–152.
110. Bhowmick NA, Zent R, Ghiassi M, McDonnell M, Moses HL: **Integrin beta 1 signaling is necessary for transforming growth factor-beta activation of p38MAPK and epithelial plasticity.** *J Biol Chem* 2001, **276**:46707–46713.
111. Xie L, Law BK, Chytil AM, Brown KA, Aakre ME, Moses HL: **Activation of the Erk pathway is required for TGF-beta1-induced EMT in vitro.** *Neoplasia* 2004, **6**:603–610.
112. Porsch H, Bernert B, Mehic M, Theocharis AD, Heldin CH, Heldin P: **Efficient TGFbeta-induced epithelial-mesenchymal transition depends on hyaluronan synthase HAS2.** *Oncogene* 2013, **32**:4355–4365.
113. Zhang H, Liu L, Wang Y, Zhao G, Xie R, Liu C, Xiao X, Wu K, Nie Y, Fan D: **KLF8 involves in TGF-beta-induced EMT and promotes invasion and migration in gastric cancer cells.** *J Cancer Res Clin Oncol* 2013, **139**:1033–1042.
114. Ding X, Park SI, McCauley LK, Wang CY: **Signaling between transforming growth factor beta (TGF-beta) and transcription factor SNAI2 represses expression of microRNA miR-203 to promote epithelial-mesenchymal transition and tumor metastasis.** *J Biol Chem* 2013, **288**:10241–10253.
115. Bhowmick NA, Ghiassi M, Bakin A, Aakre M, Lundquist CA, Engel ME, Arteaga CL, Moses HL: **Transforming growth factor-beta1 mediates epithelial to mesenchymal transdifferentiation through a RhoA-dependent mechanism.** *Mol Biol Cell* 2001, **12**:27–36.
116. Bandyopadhyay A, Raghavan S: **Defining the role of integrin alphavbeta6 in cancer.** *Curr Drug Targets* 2009, **10**:645–652.
117. Munger JS, Huang X, Kawakatsu H, Griffiths MJ, Dalton SL, Wu J, Pittet JF, Kaminski N, Garat C, Matthay MA, Rifkin DB, Sheppard D: **The integrin alpha v beta 6 binds and activates latent TGF beta 1: a mechanism for regulating pulmonary inflammation and fibrosis.** *Cell* 1999, **96**:319–328.
118. Giacomini MM, Travis MA, Kudo M, Sheppard D: **Epithelial cells utilize cortical actin/myosin to activate latent TGF-beta through integrin alpha (v)beta(6)-dependent physical force.** *Exp Cell Res* 2012, **318**:716–722.
119. Wipff PJ, Rifkin DB, Meister JJ, Hinz B: **Myofibroblast contraction activates latent TGF-beta1 from the extracellular matrix.** *J Cell Biol* 2007, **179**:1311–1323.
120. Tan JL, Tien J, Pirone DM, Gray DS, Bhadriraju K, Chen CS: **Cells lying on a bed of microneedles: an approach to isolate mechanical force.** *Proc Natl Acad Sci U S A* 2003, **100**:1484–1489.
121. Thoeelking G, Reiss B, Wegener J, Oberleithner H, Pavenstaedt H, Riethmuller C: **Nanotopography follows force in TGF-beta1 stimulated epithelium.** *Nanotechnology* 2010, **21**:265102.
122. Buckley ST, Medina C, Davies AM, Ehrhardt C: **Cytoskeletal re-arrangement in TGF-beta1-induced alveolar epithelial-mesenchymal transition studied by atomic force microscopy and high-content analysis.** *Nanomedicine* 2012, **8**:355–364.
123. Schneider D, Baronsky T, Pietuch A, Rother J, Oelkers M, Fichtner D, Wedlich D, Janshoff A: **Tension monitoring during epithelial-to-mesenchymal transition links the switch of phenotype to expression of moesin and cadherins in NMuMG cells.** *PLoS One* 2013, **8**:e80068.
124. Arnoux V, Come C, Kusewitt D, Hudson L, Savagner P: **Cutaneous wound reepithelialization: A partial and reversible EMT.** In *Rise and fall of epithelial phenotype: Concepts of epithelial-mesenchymal transition*. Edited by Savagner P. Berlin: Springer; 2005:111–134.
125. Wagh AA, Roan E, Chapman KE, Desai LP, Rendon DA, Eckstein EC, Waters CM: **Localized elasticity measured in epithelial cells migrating at a wound edge using atomic force microscopy.** *Am J Physiol Lung Cell Mol Physiol* 2008, **295**:L54–L60.
126. Watanabe T, Takahashi Y: **Tissue morphogenesis coupled with cell shape changes.** *Curr Opin Genet Devel* 2010, **20**:443–447.
127. Locascio A, Nieto MA: **Cell movements during vertebrate development: integrated tissue behaviour versus individual cell migration.** *Curr Opin Genet Devel* 2001, **11**:464–469.
128. Chen CS, Mrksich M, Huang S, Whitesides GM, Ingber DE: **Geometric control of cell life and death.** *Science* 1997, **276**:1425–1428.
129. Folkman J, Moscona A: **Role of cell shape in growth control.** *Nature* 1978, **273**:345–349.
130. Watt FM, Jordan PW, Oneill CH: **Cell-shape controls terminal differentiation of human epidermal-keratinocytes.** *Proc Natl Acad Sci U S A* 1988, **85**:5576–5580.
131. Roskelley CD, Desprez PY, Bissell MJ: **Extracellular matrix-dependent tissue-specific gene expression in mammary epithelial cells requires both physical and biochemical signal transduction.** *Proc Natl Acad Sci U S A* 1994, **91**:12378–12382.
132. McBeath R, Pirone DM, Nelson CM, Bhadriraju K, Chen CS: **Cell shape, cytoskeletal tension, and RhoA regulate stem cell lineage commitment.** *Dev Cell* 2004, **6**:483–495.
133. Connelly JT, Gautrot JE, Trappmann B, Tan DW, Donati G, Huck WT, Watt FM: **Actin and serum response factor transduce physical cues from the microenvironment to regulate epidermal stem cell fate decisions.** *Nat Cell Biol* 2010, **12**:711–718.
134. Paluch E, Heisenberg C-P: **Biology and physics of cell shape changes in development.** *Curr Biol* 2009, **19**:R790–R799.
135. Lecuit T, Lenne PF: **Cell surface mechanics and the control of cell shape, tissue patterns and morphogenesis.** *Nat Rev Mol Cell Biol* 2007, **8**:633–644.
136. Hautmann MB, Adam PJ, Owens GK: **Similarities and differences in smooth muscle alpha-actin induction by TGF-beta in smooth muscle versus non-smooth muscle cells.** *Arterioscler Thromb Vasc Biol* 1999, **19**:2049–2058.
137. Selvaraj A, Prywes R: **Expression profiling of serum inducible genes identifies a subset of SRF target genes that are MKL dependent.** *BMC Mol Biol* 2004, **5**:13.
138. Fan L, Sebe A, Peterfi Z, Masszi A, Thirone AC, Rotstein OD, Nakano H, McCulloch CA, Szaszi K, Mucsi I, Kapus A: **Cell contact-dependent regulation of epithelial-myofibroblast transition via the rho-rho kinase-phospho-myosin pathway.** *Mol Biol Cell* 2007, **18**:1083–1097.
139. Small EM, Thatcher JE, Sutherland LB, Kinoshita H, Gerard RD, Richardson JA, Dimairo JM, Sadek H, Kuwahara K, Olson EN: **Myocardin-related transcription factor-a controls myofibroblast activation and fibrosis in response to myocardial infarction.** *Circ Res* 2010, **107**:294–304.
140. Medjkane S, Perez-Sanchez C, Gaggioli C, Sahai E, Treisman R: **Myocardin-related transcription factors and SRF are required for cytoskeletal dynamics and experimental metastasis.** *Nat Cell Biol* 2009, **11**:257–268.
141. Miralles F, Posern G, Zaromytidou AI, Treisman R: **Actin dynamics control SRF activity by regulation of its coactivator MAL.** *Cell* 2003, **113**:329–342.
142. Engler AJ, Sen S, Sweeney HL, Discher DE: **Matrix elasticity directs stem cell lineage specification.** *Cell* 2006, **126**:677–689.
143. Georges PC, Hui JJ, Gombos Z, McCormick ME, Wang AY, Uemura M, Mick R, Janmey PA, Furth EE, Wells RG: **Increased stiffness of the rat liver precedes matrix deposition: implications for fibrosis.** *Am J Physiol Gastrointest Liver Physiol* 2007, **293**:G1147–G1154.
144. Levental KR, Yu H, Kass L, Lakins JN, Egeblad M, Erler JT, Fong SF, Csiszar K, Giaccia A, Weninger W, Yamauchi M, Gasser DL, Weaver VM: **Matrix crosslinking forces tumor progression by enhancing integrin signaling.** *Cell* 2009, **139**:891–906.
145. Paszek MJ, Zahir N, Johnson KR, Lakins JN, Rozenberg GI, Gefen A, Reinhart-King CA, Margulies SS, Dembo M, Boettiger D, Hammer DA, Weaver VM: **Tensional homeostasis and the malignant phenotype.** *Cancer Cell* 2005, **8**:241–254.
146. Hinz B: **The myofibroblast: paradigm for a mechanically active cell.** *J Biomech* 2010, **43**:146–155.
147. Brown AC, Fiore VF, Sulchek TA, Barker TH: **Physical and chemical microenvironmental cues orthogonally control the degree and duration of fibrosis-associated epithelial-to-mesenchymal transitions.** *J Pathol* 2013, **229**:25–35.
148. Hinz B: **Tissue stiffness, latent TGF-β1 activation, and mechanical signal transduction: implications for the pathogenesis and treatment of fibrosis.** *Curr Rheumatol Rep* 2009, **11**:120–126.

149. Levental I, Levental KR, Klein EA, Assoian R, Miller RT, Wells RG, Janmey PA: **A simple indentation device for measuring micrometer-scale tissue stiffness.** *J Phys Condens Matter* 2010, **22**:194120.
150. Liu F, Mih JD, Shea BS, Kho AT, Sharif AS, Tager AM, Tschumperlin DJ: **Feedback amplification of fibrosis through matrix stiffening and COX-2 suppression.** *J Cell Biol* 2010, **190**:693–706.
151. Wells RG: **Tissue mechanics and fibrosis.** *Biochimica et Biophysica Acta* 2013, **1832**:884–890.
152. Provenzano PP, Inman DR, Eliceiri KW, Knittel JG, Yan L, Rueden CT, White JG, Keely PJ: **Collagen density promotes mammary tumor initiation and progression.** *BMC Med* 2008, **6**:11.
153. Lopez JI, Kang I, You WK, McDonald DM, Weaver VM: **In situ force mapping of mammary gland transformation.** *Integr Biol (Camb)* 2011, **3**:910–921.
154. Boyd NF, Lockwood GA, Byng JW, Tritchler DL, Yaffe MJ: **Mammographic densities and breast cancer risk.** *Cancer Epidemiol Biomarkers Prev* 1998, **7**:1133–1144.
155. Yaffe MJ, Boyd NF, Byng JW, Jong RA, Fishell E, Lockwood GA, Little LE, Tritchler DL: **Breast cancer risk and measured mammographic density.** *Eur J Cancer Prev* 1998, **7**(Suppl 1):S47–S55.
156. Markowski MC, Brown AC, Barker TH: **Directing epithelial to mesenchymal transition through engineered microenvironments displaying orthogonal adhesive and mechanical cues.** *J Biomed Mater Res A* 2012, **100**:2119–2127.
157. Brabletz T, Jung A, Reu S, Porzner M, Hlubek F, Kunz-Schughart LA, Knuechel R, Kirchner T: **Variable beta-catenin expression in colorectal cancers indicates tumor progression driven by the tumor environment.** *Proc Natl Acad Sci U S A* 2001, **98**:10356–10361.
158. Jung A, Schrauder M, Oswald U, Knoll C, Sellberg P, Palmqvist R, Niedobitek G, Brabletz T, Kirchner T: **The invasion front of human colorectal adenocarcinomas shows co-localization of nuclear beta-catenin, cyclin D1, and p16INK4A and is a region of low proliferation.** *Am J Pathol* 2001, **159**:1613–1617.
159. Nelson CM, Jean RP, Tan JL, Liu WF, Sniadecki NJ, Spector AA, Chen CS: **Emergent patterns of growth controlled by multicellular form and mechanics.** *Proc Natl Acad Sci U S A* 2005, **102**:11594–11599.
160. Sato M, Muragaki Y, Saika S, Roberts AB, Ooshima A: **Targeted disruption of TGF-beta1/Smad3 signaling protects against renal tubulointerstitial fibrosis induced by unilateral ureteral obstruction.** *J Clin Invest* 2003, **112**:1486–1494.
161. Heise RL, Stober V, Cheluvuvaraju C, Hollingsworth JW, Garantzotis S: **Mechanical stretch induces epithelial-mesenchymal transition in alveolar epithelia via hyaluronan activation of innate immunity.** *J Biol Chem* 2011, **286**:17435–17444.
162. Chan SW, Lim CJ, Guo K, Ng CP, Lee I, Hunziker W, Zeng Q, Hong W: **A role for TAZ in migration, invasion, and tumorigenesis of breast cancer cells.** *Cancer Res* 2008, **68**:2592–2598.
163. Mitani A, Nagase T, Fukuchi K, Aburatani H, Makita R, Kurihara H: **Transcriptional coactivator with PDZ-binding motif is essential for normal alveolarization in mice.** *Am J Respir Crit Care Med* 2009, **180**:326–338.
164. Harvey KF, Zhang X, Thomas DM: **The Hippo pathway and human cancer.** *Nat Rev Cancer* 2013, **13**:246–257.
165. Johnson R, Halder G: **The two faces of Hippo: targeting the Hippo pathway for regenerative medicine and cancer treatment.** *Nat Rev Drug Discov* 2014, **13**:63–79.
166. Varelas X, Sakuma R, Samavarchi-Tehrani P, Peerani R, Rao BM, Dembowy J, Yaffe MB, Zandstra PW, Wrana JL: **TAZ controls Smad nucleocytoplasmic shuttling and regulates human embryonic stem-cell self-renewal.** *Nat Cell Biol* 2008, **10**:837–848.
167. Varelas X, Samavarchi-Tehrani P, Narimatsu M, Weiss A, Cockburn K, Larsen BG, Rossant J, Wrana JL: **The Crumbs complex couples cell density sensing to Hippo-dependent control of the TGF-beta-SMAD pathway.** *Dev Cell* 2010, **19**:831–844.
168. Dupont S, Morsut L, Aragona M, Enzo E, Giulitti S, Cordenonsi M, Zanconato F, Le Digabel J, Forcato M, Bicciato S, Elvassore N, Piccolo S: **Role of YAP/TAZ in mechanotransduction.** *Nature* 2011, **474**:179–183.
169. Halder G, Dupont S, Piccolo S: **Transduction of mechanical and cytoskeletal cues by YAP and TAZ.** *Nat Rev Mol Cell Biol* 2012, **13**:591–600.
170. Sun Y, Yong KM, Villa-Diaz LG, Zhang X, Chen W, Philson R, Weng S, Xu H, Krebsbach PH, Fu J: **Hippo/YAP-mediated rigidity-dependent motor neuron differentiation of human pluripotent stem cells.** *Nat Mater* 2014, **13**:599–604.
171. Aragona M, Panciera T, Manfrin A, Giulitti S, Michieli F, Elvassore N, Dupont S, Piccolo S: **A mechanical checkpoint controls multicellular growth through YAP/TAZ regulation by actin-processing factors.** *Cell* 2013, **154**:1047–1059.
172. Speight P, Nakano H, Kelley TJ, Hinzb, Kapus A: **Differential topical susceptibility to TGFbeta in intact and injured regions of the epithelium: key role in myofibroblast transition.** *Mol Biol Cell* 2013, **24**:3326–3336.
173. Lei QY, Zhang H, Zhao B, Zha ZY, Bai F, Pei XH, Zhao S, Xiong Y, Guan KL: **TAZ promotes cell proliferation and epithelial-mesenchymal transition and is inhibited by the hippo pathway.** *Mol Cell Biol* 2008, **28**:2426–2436.
174. Mana-Capelli S, Paramasivam M, Dutta S, McCollum D: **Angiomotins link F-actin architecture to Hippo pathway signaling.** *Mol Biol Cell* 2014, **25**:1676–1685.
175. Chua KN, Ma J, Thiery JP: **Targeted therapies in control of EMT in carcinoma and fibrosis.** *Drug Discov Today* 2008, **4**:261–267.
176. Connolly EC, Freimuth J, Akhurst RJ: **Complexities of TGF-beta targeted cancer therapy.** *Int J Biol Sci* 2012, **8**:964–978.
177. Akhurst RJ, Hata A: **Targeting the TGFbeta signalling pathway in disease.** *Nat Rev Drug Discov* 2012, **11**:790–811.
178. Biswas S, Guix M, Rinehart C, Dugger TC, Chytil A, Moses HL, Freeman ML, Arteaga CL: **Inhibition of TGF-beta with neutralizing antibodies prevents radiation-induced acceleration of metastatic cancer progression.** *J Clin Invest* 2007, **117**:1305–1313.
179. Biswas S, Nyman JS, Alvarez J, Chakrabarti A, Ayres A, Sterling J, Edwards J, Rana T, Johnson R, Perrien DS, Lonning S, Shyr Y, Matrisian LM, Mundy GR: **Anti-transforming growth factor beta antibody treatment rescues bone loss and prevents breast cancer metastasis to bone.** *PLoS One* 2011, **6**:e27090.
180. Nam JS, Terabe M, Mamura M, Kang MJ, Chae H, Stuelten C, Kohn E, Tang B, Sabzevari H, Anver MR, Lawrence S, Danielpour D, Lonning S, Berzofsky JA, Wakefield LM: **An anti-transforming growth factor beta antibody suppresses metastasis via cooperative effects on multiple cell compartments.** *Cancer Res* 2008, **68**:3835–3843.
181. Ganapathy V, Ge R, Grazioli A, Xie W, Banach-Petrosky W, Kang Y, Lonning S, McPherson J, Yingling JM, Biswas S, Mundy GR, Reiss M: **Targeting the transforming growth factor-beta pathway inhibits human basal-like breast cancer metastasis.** *Mol Cancer* 2010, **9**:122.
182. Bouquet F, Pal A, Pilonis KA, Demaria S, Hann B, Akhurst RJ, Babb JS, Lonning SM, DeWynngaert JK, Formenti SC, Barcellos-Hoff MH: **TGFbeta1 inhibition increases the radiosensitivity of breast cancer cells in vitro and promotes tumor control by radiation in vivo.** *Clin Cancer Res* 2011, **17**:6754–6765.
183. Crunkhorn S: **Deal watch: Biogen acquires Stromedix to pursue novel fibrosis therapy.** *Nat Rev Drug Discov* 2012, **11**:260.
184. Katsumoto TR, Violette SM, Sheppard D: **Blocking TGFbeta via inhibition of the alphavbeta6 integrin: a possible therapy for systemic sclerosis interstitial lung disease.** *Int J Rheumatol* 2011, **2011**:208219.
185. Horan GS, Wood S, Ona V, Li DJ, Lukashev ME, Weinreb PH, Simon KJ, Hahm K, Allaire NE, Rinaldi NJ, Goyal J, Feghali-Bostwick CA, Matteson EL, O'Hara C, Lafyatis R, Davis GS, Huang X, Sheppard D, Violette SM: **Partial inhibition of integrin alpha(v)beta6 prevents pulmonary fibrosis without exacerbating inflammation.** *Am J Respir Crit Care Med* 2008, **177**:56–65.
186. Puthawala K, Hadjiangelis N, Jacoby SC, Bayongan E, Zhao Z, Yang Z, Devitt ML, Horan GS, Weinreb PH, Lukashev ME, Violette SM, Grant KS, Colarossi C, Formenti SC, Munger JS: **Inhibition of integrin alpha(v)beta6, an activator of latent transforming growth factor-beta, prevents radiation-induced lung fibrosis.** *Am J Respir Crit Care Med* 2008, **177**:82–90.
187. Van Aarsen LA, Leone DR, Ho S, Dolinski BM, McCoon PE, LePage DJ, Kelly R, Heaney G, Rayhorn P, Reid C, Simon KJ, Horan GS, Tao N, Gardner HA, Skelly MM, Gown AM, Thomas GJ, Weinreb PH, Fawell SE, Violette SM: **Antibody-mediated blockade of integrin alpha v beta 6 inhibits tumor progression in vivo by a transforming growth factor-beta-regulated mechanism.** *Cancer Res* 2008, **68**:561–570.
188. Cheng HC, Ho TC, Chen SL, Lai HY, Hong KF, Tsao YP: **Troglitazone suppresses transforming growth factor beta-mediated fibrogenesis in retinal pigment epithelial cells.** *Mol Vis* 2008, **14**:95–104.
189. Kawai T, Masaki T, Doi S, Arakawa T, Yokoyama Y, Doi T, Kohno N, Yorioka N: **PPAR-gamma agonist attenuates renal interstitial fibrosis and inflammation through reduction of TGF-beta.** *Lab Invest* 2009, **89**:47–58.

190. Jeon KI, Kulkarni A, Woeller CF, Phipps RP, Sime PJ, Hindman HB, Huxlin KR: **Inhibitory effects of PPARgamma ligands on TGF-beta1-induced corneal myofibroblast transformation.** *Am J Path* 2014, **184**:1429–1445.
191. Evelyn CR, Wade SM, Wang Q, Wu M, Iniguez-Lluhi JA, Merajver SD, Neubig RR: **CCG-1423: a small-molecule inhibitor of RhoA transcriptional signaling.** *Mol Cancer Ther* 2007, **6**:2249–2260.
192. Evelyn CR, Bell JL, Ryu JG, Wade SM, Kocab A, Harzdorf NL, Showalter HD, Neubig RR, Larsen SD: **Design, synthesis and prostate cancer cell-based studies of analogs of the Rho/MKL1 transcriptional pathway inhibitor, CCG-1423.** *Bioorg Med Chem Lett* 2010, **20**:665–672.
193. Hayashi K, Watanabe B, Nakagawa Y, Minami S, Morita T: **RPEL proteins are the molecular targets for CCG-1423, an inhibitor of Rho signaling.** *PLoS One* 2014, **9**:e89016.
194. Johnson LA, Rodansky ES, Haak AJ, Larsen SD, Neubig RR, Higgins PDR: **Novel Rho/MRTF/SRF inhibitors block matrix-stiffness and TGF-beta-induced fibrogenesis in human colonic myofibroblasts.** *Inflamm Bowel Dis* 2014, **20**:154–165.
195. Velasquez LS, Sutherland LB, Liu Z, Grinnell F, Kamm KE, Schneider JW, Olson EN, Small EM: **Activation of MRTF-A-dependent gene expression with a small molecule promotes myofibroblast differentiation and wound healing.** *Proc Natl Acad Sci U S A* 2013, **110**:16850–16855.
196. Zeisberg M, Bottiglio C, Kumar N, Maeshima Y, Strutz F, Muller GA, Kalluri R: **Bone morphogenic protein-7 inhibits progression of chronic renal fibrosis associated with two genetic mouse models.** *Am J Physiol Renal Physiol* 2003, **285**:F1060–F1067.
197. Chua KN, Sim WJ, Racine V, Lee SY, Goh BC, Thiery JP: **A cell-based small molecule screening method for identifying inhibitors of epithelial-mesenchymal transition in carcinoma.** *PLoS One* 2012, **7**:e33183.

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