F1000Research

CrossMark
← click for updates

REVIEW

The myofibroblast in wound healing and fibrosis: answered and unanswered questions [version 1; referees: 2 approved]

Marie-Luce Bochaton-Piallat[1], Giulio Gabbiani[1], Boris Hinz[2]

[1]Department of Pathology and Immunology, Faculty of Medicine, University of Geneva, Geneva, Switzerland
[2]Laboratory of Tissue Repair and Regeneration, Matrix Dynamics Group, Faculty of Dentistry, University of Toronto, Toronto, Canada

Abstract

The discovery of the myofibroblast has allowed definition of the cell responsible for wound contraction and for the development of fibrotic changes. This review summarizes the main features of the myofibroblast and the mechanisms of myofibroblast generation. Myofibroblasts originate from a variety of cells according to the organ and the type of lesion. The mechanisms of myofibroblast contraction, which appear clearly different to those of smooth muscle cell contraction, are described. Finally, we summarize the possible strategies in order to reduce myofibroblast activities and thus influence several pathologies, such as hypertrophic scars and organ fibrosis.

This article is included in the F1000 Faculty Reviews channel.

Open Peer Review

Referee Status: ☑☑

	Invited Referees	
	1	**2**
version 1 published 26 Apr 2016	☑	☑

F1000 Faculty Reviews are commissioned from members of the prestigious F1000 Faculty. In order to make these reviews as comprehensive and accessible as possible, peer review takes place before publication; the referees are listed below, but their reports are not formally published.

1 **Jack Gauldie**, McMaster University Canada

2 **Steven E. Wilson**, Cleveland Clinic USA

Discuss this article

Comments (0)

Corresponding author: Marie-Luce Bochaton-Piallat (marie-luce.piallat@unige.ch)

Competing interests: The authors declare that they have no competing interests.

Introduction

Wound healing has interested the medical praxis since the beginning of human history, but for many centuries the effort of physicians has concentrated more on empirical therapeutic strategies rather than on the understanding of its biological mechanisms. During the last few centuries, however, a gradual progress has been achieved in defining and understanding several physiological aspects of wound healing. In particular, the formation and evolution of granulation tissue has been described in the second half of the 18th century, mainly thanks to the British surgeon John Hunter, and in the last century it has been shown that wound contraction is due to an active contraction of granulation tissue, mainly thanks to the work of the French surgeon Alexis Carrel[1]. The discovery of the myofibroblast more than forty years ago allowed the identification of the cell responsible for this phenomenon[2]. This coincided with the early establishment of the cytoskeleton concept[3]. The myofibroblast was then considered to be a contractile non-muscle cell[4]. Since the first description, our knowledge of myofibroblast structure and activity has progressed enormously. The purpose of this article is to briefly summarize the biological features of the myofibroblast and to discuss some of the promising strategies to suppress this cell's activity in order to achieve the possibility of influencing important pathological situations, such as fibrotic lesions, that presently cannot be cured successfully.

Evolution of the myofibroblast concept

Initially, the myofibroblast was described by means of electron microscopy revealing the presence of prominent cytoplasmic microfilament bundles and peripheral focal adhesions in the fibroblastic cells of granulation tissue[2]. Electron microscopy further showed the existence of gap junctions connecting myofibroblasts, thus reinforcing the suggestion of similarity between myofibroblasts and smooth muscle (SM) cells[5]. The production of a specific antibody against α-SM actin, the actin isoform typical of vascular SM cells, allowed the demonstration that myofibroblasts express α-SM actin and are hence equipped with a typical SM protein[6].

In the early phases of granulation tissue formation after the production of a wound, local fibroblasts begin moving from the unaffected dermis and subcutaneous tissue toward the wound center and acquire bundles of microfilaments, similar to *in vitro* stress fibers, containing only β- and γ-cytoplasmic actins; these cells have been named proto-myofibroblasts and evolve generally into α-SM actin containing differentiated myofibroblasts that are responsible for wound contraction[7]. When the wound closes, myofibroblasts disappear through apoptosis[8], and a scar persists in the affected area. When myofibroblasts persist in a closed wound, they indicate the development of a hypertrophic scar, an important pathological evolution of wound healing, particularly frequent after burn injury[7,9]. Myofibroblasts are also present in all fibrotic diseases, such as scleroderma, as well as liver, kidney, and lung fibrosis and are prominent in heart failure and repair after myocardial infarction. Finally, myofibroblasts are the main components of the stromal reaction to several epithelial tumors[7,10]. It should be noted that both proto-myofibroblasts and differentiated myofibroblasts can be found in normal tissues, for example in lung alveolar septa and at the periphery of intestinal crypts, respectively[7], where they probably exert physiological mechanical functions.

Much work has been performed in order to find specific markers of the myofibroblastic phenotype. As stated above, α-SM actin discriminates myofibroblasts from fibroblasts and has become the most used marker for this cell. Several other markers have been proposed, but no specific marker has been identified until now. However, several SM cell markers are not expressed in myofibroblasts, such as SM myosin heavy chains, h-caldesmon, and smoothelin[11]; this underlines the functional differences between the two cells, as we shall discuss below.

Mechanisms of myofibroblast formation and evolution

After a wounding insult, blood extravasation and clot formation occur followed by an inflammatory phase that allows an accumulation of blood-borne cells, liberating many cytokines and growth factors essential for the onset of the following phase of granulation tissue formation[12]. In early granulation tissue, motile proto-myofibroblasts appear and start to synthesize extracellular matrix (ECM) components, such as collagen type I and III[7]. Another relevant new component of ECM is cellular fibronectin, which contains the alternatively spliced segments EDA (or EIIIA) and EDB (or EIIIB) and is present in connective tissue during development but reappears in pathological situations such as granulation tissue and fibrotic lesions[13,14]. EDA fibronectin has been shown to be essential for the differentiation of myofibroblasts[15]. The early transformation of fibroblasts into proto-myofibroblasts appears to depend on the mechanical changes taking place in the wound compared to the normal skin, in particular increased stiffness[7,16]; moreover, platelet-derived growth factor has been shown to stimulate proto-myofibroblast motility[17]. The development of α-SM actin synthesizing differentiated myofibroblasts is essentially due to the action of transforming growth factor (TGF)-β1 in the presence of EDA fibronectin[15,18]. TGF-β1 is present in the ECM as a large latent complex including latency-associated peptide and latent TGF-β1-binding protein[9]. It can be liberated by proteolytic enzymes as well as by integrin-dependent mechanically induced mechanisms[9]. The force exerted by stress fibers through transmembrane integrins is enough to free TGF-β1 from the large latent complex, and the strained ECM is capable of maintaining a feedback mechanism, assuring a persistent fibrotic activity by the myofibroblast[19,20]; moreover, straining and/or stiffening of the ECM can increase the availability of TGF-β1[21,22] (Figure 1). Straining and stiffening are consequences of fibroblast and myofibroblast remodeling activities. Matrix stiffening is additionally promoted by fibroblast and inflammatory cell-derived collagen crosslinking enzymes including lysyl oxidases and lysyl oxidase-like enzymes, as reviewed in 20,23. The incorporation of α-SM actin into stress fibers has been shown to significantly increase the contractile activity of fibroblasts[24]; the force generated by myofibroblast stress fibers is transmitted to the ECM through focal adhesions that contain specialized transmembrane integrins[25]. As stated above, myofibroblasts disappear when a wound closes, mainly through apoptosis[8]. The mechanisms of apoptosis induction, or conversely of myofibroblast persistence, in hypertrophic scars are not clarified; however, the importance of a focal adhesion complex component, Hic-5, a paxillin homologue, in maintaining the myofibroblast phenotype has been demonstrated[26]. Moreover, myofibroblasts can disappear by means of accelerated senescence[27] and even, at least in some instances, revert to the normal phenotype[28].

relaxed matrix - normal

pre-stressed matrix - fibrotic
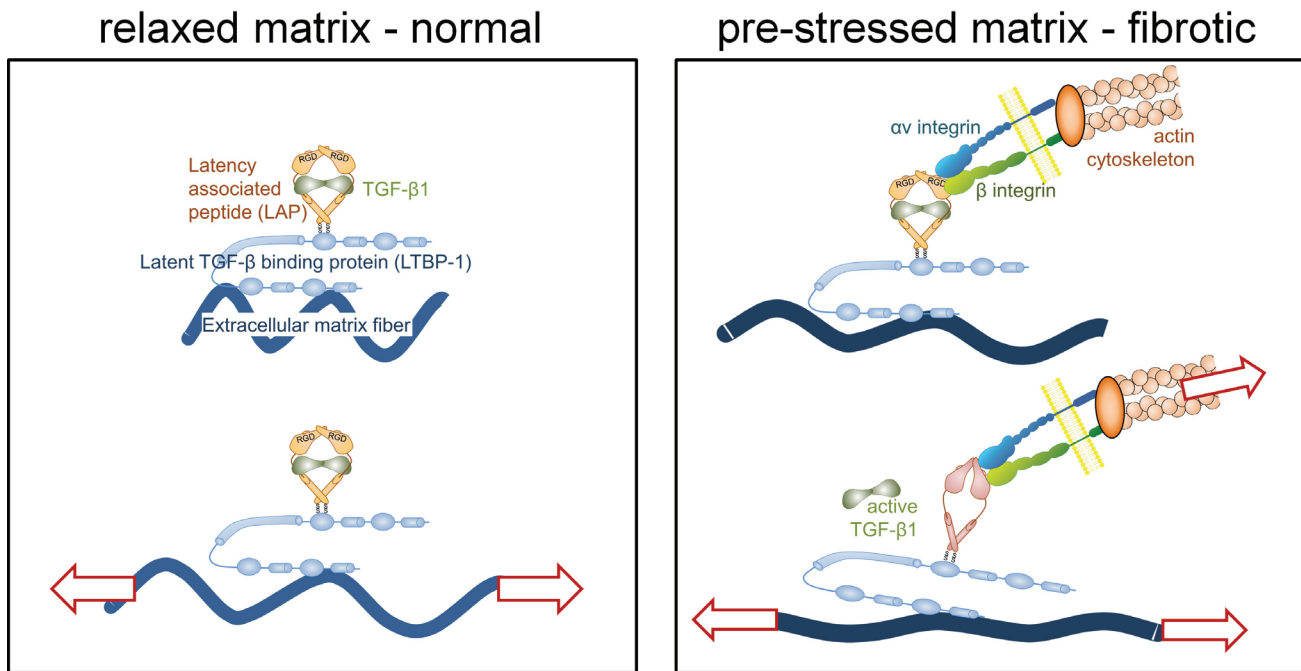
Figure 1. Mechanical activation of TGF-β1. In normal connective tissue, loosely arranged collagen protects resident fibroblasts and latent transforming growth factor (TGF)-β1 complexes from being strained with the extracellular matrix (ECM). Fibroblasts in normal tissue do not express or present the integrin receptors that bind and activate latent TGF-β1. During tissue repair and in organ fibrosis, activated myofibroblasts express αv integrins that connect the contractile actin/myosin cytoskeleton to latent TGF-β1. The accumulation of collagen and its excessive remodeling (crosslinking) by these myofibroblasts result in denser and straighter ECM fibers, which leads to overall higher tissue stiffness. Because ECM fibers are straighter, even smaller strains applied to the fibrotic ECM externally, or by residing myofibroblasts, will be sufficient for the release of active TGF-β1 (modified from Hinz B and Suki B [2016] *Does breathing amplify fibrosis?* Editorial on 21).

Mechanism of myofibroblast contraction and mechanotransduction

The initial studies suggesting a similarity between myofibroblast and SM cell contractile activities[4] were gradually reconsidered in light of the consideration of the different functional activities of the two cells: SM cell contraction is rapid and short in duration, whereas myofibroblast contraction is rather long lasting and results in a permanent tissue retraction, probably stabilized by ECM deposition[7]. Evidence has gradually accumulated suggesting that, in addition to the classical calcium-calmodulin-myosin light chain kinase-dependent SM cell contraction mechanism[11], myofibroblast contractile activity can be regulated by the activation of the Rho/ROCK/myosin light chain phosphatase pathway[7,29–31]. This long-duration type of contraction underlines an essential difference between the SM cell and the myofibroblast and could explain the characteristic tissue remodeling activity of this cell.

The forces generated by the contractile activity of myofibroblasts are transmitted to the surrounding ECM through specialized focal adhesions containing transmembrane integrins. As a result, strained and more compacted ECM develops. Interestingly, the mechanical conditions generated by the myofibroblast feedback leads to their sustained pro-fibrotic activity[10,19]. More recently, it has been shown that megakaryoblastic leukemia factor 1 (MKL1),

also named myocardin-related transcription factor (MRTF), is crucial for myofibroblast differentiation and mechanotransduction. In various myofibroblast precursor cells, it links mechanical stress to the transcriptional activity of muscle-cell genes via the polymerization state of actin[32–36]. Inhibition of MRTF reduces experimentally induced skin fibrosis in rodents[37], as well as differentiation of human colonic myofibroblasts[38]. Similarly, YAP/TAZ transcription factors, known to mediate mechano-responses[39], positively regulate myofibroblast activation[40–44].

Myofibroblast origin

One of the intriguing features of the myofibroblast is that it can derive from a large variety of cell types. As stated above, mesenchymal cells with myofibroblastic features are present in normal tissues, including the uterine submucosa, follicles of lymph nodes and spleen, intestinal villous cores and crypts, theca externa of the ovary, periodontal ligament, adrenal capsule, lung septa, and bone marrow stroma[7]. It appears more and more evident that the term fibroblast comprises a heterogeneous cell population[10,45], thus it is possible that only some specialized fibroblastic cells generate myofibroblasts in normal and pathological situations, as recently supported by studies on skin and heart fibrosis[46–48]. During pathological situations, local fibroblasts allegedly represent the major source of myofibroblastic cells[10]; however, in particular

cases, other local cells become the main precursors, such as SM cells in coronary atheromatous plaque[49], keratocytes in the eye[50,51], perisinusoidal cells in the liver[52], and pericytes in many organs[53–55]. In addition, myofibroblasts may develop through the process of epithelial-mesenchymal transition[56,57] or endothelial-mesenchymal transition[58]. Finally, myofibroblasts may derive from circulating bone marrow-derived specialized inflammatory cells called fibrocytes and participate in fibrotic lesions in several organs[59,60]. Circulating and/or resident mesenchymal stromal/stem cells (MSCs) are prominent precursors of myofibroblasts in a variety of organs and injury situations[61,62]. Because delivery of MSCs is an attractive approach to regenerate organs that are beyond repair within the body's own capacity[63,64], understanding MSC-to-myofibroblast activation (fibrogenesis) will be of particular importance for the success of MSC therapies[40,65].

There is considerable variability and dispute in the literature concerning the proportions of different precursor cells contributing to the myofibroblast pool. However, different research groups seem to generally agree that myofibroblast sources can differ between different individuals, organs, animals, or particular injury models. For example, in the corneal fibrosis model, 30 to 70% of myofibroblasts are derived from bone marrow-derived precursors depending on the type of wound and the individual that is wounded (reviewed in 51). Thus, using drugs that modulate myofibroblast activation from specific precursor cells can be an effective strategy to inhibit fibrosis in an organ-specific manner.

Perspectives

As we have seen, the myofibroblast represents an eclectic cell whose major function appears to be the remodeling of connective tissue. If we consider the variety of its possible origins, the myofibroblast could be defined as a phenotypic variant of many cell types, developing upon the appearance of appropriate stimuli. Myofibroblast activity can be physiological, e.g., regulation of ventilation/perfusion ratio in pulmonary alveoli, and useful for wound healing but noxious in many pathological situations, e.g., fibrotic lesions[7].

Despite many attempts and despite the clinical importance of fibrotic lesions[9,12], there is not at present any clinically accepted pharmacological tool capable of influencing myofibroblast activity and thus the evolution of these diseases. We shall discuss some strategies that could possibly lead to the development of efficient tools. Despite the heterogeneity of origin, all differentiated myofibroblasts perform the same functions, i.e. tissue remodeling and synthesis of ECM. Hence, the processes regulating these functions appear to represent promising targets of therapeutic strategies. TGF-β1 would appear as an ideal target in order to control myofibroblast activity. Unfortunately, until now no relevant results have been obtained by using direct inhibitors; however, several pathways of TGF-β1 action remain to be explored and a number of

clinical trials that target TGF-β1 are pending[66]. EDA fibronectin is necessary for myofibroblast differentiation[15] and its absence results in wound healing or pulmonary fibrosis reduction[67], suggesting that EDA fibronectin could be addressed as a therapeutic target. The observation that α-SM actin is essential for the remodeling activity of the myofibroblast and the finding that its N-terminal peptide Ac-EEED is essential for α-SM actin incorporation into stress fibers[68] have suggested that this peptide could represent a tool for decreasing myofibroblast activity. This possibility has been demonstrated *in vitro* and in rat wound healing[69], suggesting that this peptide or, possibly more efficiently, a mimetic compound could be used therapeutically. The recent observation that tropomyosin 1.6/7 isoforms play an essential role in the stable incorporation of α-SM actin into fibroblast stress fibers[70] points to a new target for the reduction of α-SM actin expression in myofibroblasts with the consequent reduction of their remodeling activity[71]. Another way to regulate myofibroblast remodeling activity could be the control of the Rho/ROCK/myosin light chain phosphatase pathway. In this respect, it has been shown that the ROCK inhibitor Y-27632 decreases granulation tissue contraction[31]. Closely related to reducing cell contraction is the idea of blocking myofibroblast adhesion to the ECM via integrins. This will have two potential beneficial outcomes: reduced force transmission to the ECM and, provided the correct integrins are targeted, reduction of TGF-β1 activation[72,73].

Further work is needed in order to develop an efficient therapeutic approach to excessive wound healing and fibrotic diseases. Importantly, myofibroblast research will need to cross organ boundaries to exploit the full potential of drugs that are effective in one system but not studied in others. For instance, mitomycin C was shown to block fibrosis development after eye surgery[74], but its action in other organs is unknown. We feel confident that during the next few years the above-discussed strategies will allow the discovery of new, efficient tools to control these devastating diseases.

References

F F1000 recommended

1. Whipple AO: **The story of wound healing and wound repair.** Springfield, 1963.
   Reference Source

2. Gabbiani G, Ryan GB, Majno G: **Presence of modified fibroblasts in granulation tissue and their possible role in wound contraction.** *Experientia.* 1971; **27**(5): 549–50.
   PubMed Abstract | **Publisher Full Text**

3. Zampieri F, Coen M, Gabbiani G: **The prehistory of the cytoskeleton concept.** *Cytoskeleton (Hoboken).* 2014; **71**(8): 464–71.
   PubMed Abstract | **Publisher Full Text**

4. Gabbiani G, Hirschel BJ, Ryan GB, *et al.*: **Granulation tissue as a contractile organ. A study of structure and function.** *J Exp Med.* 1972; **135**(4): 719–34.
   PubMed Abstract | **Free Full Text**

5. Gabbiani G, Chaponnier C, Hüttner I: **Cytoplasmic filaments and gap junctions in epithelial cells and myofibroblasts during wound healing.** *J Cell Biol.* 1978; **76**(3): 561–8.
   PubMed Abstract | **Publisher Full Text** | **Free Full Text**

6. Skalli O, Ropraz P, Trzeciak A, *et al.*: **A monoclonal antibody against alpha-smooth muscle actin: a new probe for smooth muscle differentiation.** *J Cell Biol.* 1986; **103**(6 Pt 2): 2787–96.
   PubMed Abstract | **Publisher Full Text** | **Free Full Text**

7. Tomasek JJ, Gabbiani G, Hinz B, *et al.*: **Myofibroblasts and mechano-regulation of connective tissue remodelling.** *Nat Rev Mol Cell Biol.* 2002; **3**(5): 349–63.
   PubMed Abstract | **Publisher Full Text**

8. Desmoulière A, Redard M, Darby I, *et al.*: **Apoptosis mediates the decrease in cellularity during the transition between granulation tissue and scar.** *Am J Pathol.* 1995; **146**(1): 56–66.
   PubMed Abstract | **Free Full Text**

9. Van De Water L, Varney S, Tomasek JJ: **Mechanoregulation of the Myofibroblast in Wound Contraction, Scarring, and Fibrosis: Opportunities for New Therapeutic Intervention.** *Adv Wound Care (New Rochelle).* 2013; **2**(4): 122–41.
   PubMed Abstract | **Publisher Full Text** | **Free Full Text**

10. Hinz B, Phan SH, Thannickal VJ, *et al.*: **Recent developments in myofibroblast biology: paradigms for connective tissue remodeling.** *Am J Pathol.* 2012; **180**(4): 1340–55.
    PubMed Abstract | **Publisher Full Text** | **Free Full Text**

11. Arnoldi R, Chaponnier C, Gabbiani G, *et al.*: **Heterogeneity of Smooth Muscle.** In: Muscle: Elsevier, 2012; 1183–1195.
    Publisher Full Text

12. Wynn TA, Ramalingam TR: **Mechanisms of fibrosis: therapeutic translation for fibrotic disease.** *Nat Med.* 2012; **18**(7): 1028–40.
    PubMed Abstract | **Publisher Full Text** | **Free Full Text**

13. Brown LF, Dubin D, Lavigne L, *et al.*: **Macrophages and fibroblasts express embryonic fibronectins during cutaneous wound healing.** *Am J Pathol.* 1993; **142**(3): 793–801.
    PubMed Abstract | **Free Full Text**

14. **F** Singh P, Reimer CL, Peters JH, *et al.*: **The spatial and temporal expression patterns of integrin alpha9beta1 and one of its ligands, the EIIIA segment of fibronectin, in cutaneous wound healing.** *J Invest Dermatol.* 2004; **123**(6): 1176–81.
    PubMed Abstract | **Publisher Full Text** | **F1000 Recommendation**

15. Serini G, Bochaton-Piallat ML, Ropraz P, *et al.*: **The fibronectin domain ED-A is crucial for myofibroblastic phenotype induction by transforming growth factor-beta1.** *J Cell Biol.* 1998; **142**(3): 873–81.
    PubMed Abstract | **Publisher Full Text** | **Free Full Text**

16. **F** Goffin JM, Pittet P, Csucs G, *et al.*: **Focal adhesion size controls tension-dependent recruitment of alpha-smooth muscle actin to stress fibers.** *J Cell Biol.* 2006; **172**(2): 259–68.
    PubMed Abstract | **Publisher Full Text** | **Free Full Text** | **F1000 Recommendation**

17. Grinnell F, Petroll WM: **Cell motility and mechanics in three-dimensional collagen matrices.** *Annu Rev Cell Dev Biol.* 2010; **26**: 335–61.
    PubMed Abstract | **Publisher Full Text**

18. Desmoulière A, Geinoz A, Gabbiani F, *et al.*: **Transforming growth factor-beta 1 induces alpha-smooth muscle actin expression in granulation tissue myofibroblasts and in quiescent and growing cultured fibroblasts.** *J Cell Biol.* 1993; **122**(1): 103–11.
    PubMed Abstract | **Publisher Full Text** | **Free Full Text**

19. Duscher D, Maan ZN, Wong VW, *et al.*: **Mechanotransduction and fibrosis.** *J Biomech.* 2014; **47**(9): 1997–2005.
    PubMed Abstract | **Publisher Full Text** | **Free Full Text**

20. Hinz B: **The extracellular matrix and transforming growth factor-β1: Tale of a strained relationship.** *Matrix Biol.* 2015; **47**: 54–65.
    PubMed Abstract | **Publisher Full Text**

21. **F** Froese AR, Shimbori C, Bellaye PS, *et al.*: **Stretch Induced Activation of TGF-β1 in Pulmonary Fibrosis.** *Am J Respir Crit Care Med.* 2016.
    PubMed Abstract | **Publisher Full Text** | **F1000 Recommendation**

22. **F** Klingberg F, Chow ML, Koehler A, *et al.*: **Prestress in the extracellular matrix sensitizes latent TGF-β1 for activation.** *J Cell Biol.* 2014; **207**(2): 283–97.
    PubMed Abstract | **Publisher Full Text** | **Free Full Text** | **F1000 Recommendation**

23. Klingberg F, Hinz B, White ES: **The myofibroblast matrix: implications for tissue repair and fibrosis.** *J Pathol.* 2013; **229**(2): 298–309.
    PubMed Abstract | **Publisher Full Text** | **Free Full Text**

24. Hinz B, Celetta G, Tomasek JJ, *et al.*: **Alpha-smooth muscle actin expression upregulates fibroblast contractile activity.** *Mol Biol Cell.* 2001; **12**(9): 2730–41.
    PubMed Abstract | **Publisher Full Text** | **Free Full Text**

25. Dugina V, Fontao L, Chaponnier C, *et al.*: **Focal adhesion features during myofibroblastic differentiation are controlled by intracellular and extracellular factors.** *J Cell Sci.* 2001; **114**(Pt 18): 3285–96.
    PubMed Abstract

26. Varney SD, Betts CB, Zheng R, *et al.*: **Hic-5 is required for myofibroblast differentiation by regulating mechanically dependent MRTF-A nuclear accumulation.** *J Cell Sci.* 2016; **129**(4): 774–87.
    PubMed Abstract | **Publisher Full Text** | **Free Full Text**

27. **F** Jun JI, Lau LF: **The matricellular protein CCN1 induces fibroblast senescence and restricts fibrosis in cutaneous wound healing.** *Nat Cell Biol.* 2010; **12**(7): 676–85.
    PubMed Abstract | **Publisher Full Text** | **Free Full Text** | **F1000 Recommendation**

28. **F** Kisseleva T, Cong M, Paik Y, *et al.*: **Myofibroblasts revert to an inactive phenotype during regression of liver fibrosis.** *Proc Natl Acad Sci U S A.* 2012; **109**(24): 9448–53.
    PubMed Abstract | **Publisher Full Text** | **Free Full Text** | **F1000 Recommendation**

29. **F** Parizi M, Howard EW, Tomasek JJ: **Regulation of LPA-promoted myofibroblast contraction: role of Rho, myosin light chain kinase, and myosin light chain phosphatase.** *Exp Cell Res.* 2000; **254**(2): 210–20.
    PubMed Abstract | **Publisher Full Text** | **F1000 Recommendation**

30. **F** Anderson S, DiCesare L, Tan I, *et al.*: **Rho-mediated assembly of stress fibers is differentially regulated in corneal fibroblasts and myofibroblasts.** *Exp Cell Res.* 2004; **298**(2): 574–83.
    PubMed Abstract | **Publisher Full Text** | **F1000 Recommendation**

31. Tomasek JJ, Vaughan MB, Kropp BP, *et al.*: **Contraction of myofibroblasts in granulation tissue is dependent on Rho/Rho kinase/myosin light chain phosphatase activity.** *Wound Repair Regen.* 2006; **14**(3): 313–20.
    PubMed Abstract | **Publisher Full Text**

32. **F** Crider BJ, Risinger GM Jr, Haaksma CJ, *et al.*: **Myocardin-related transcription factors A and B are key regulators of TGF-β1-induced fibroblast to myofibroblast differentiation.** *J Invest Dermatol.* 2011; **131**(12): 2378–85.
    PubMed Abstract | **Publisher Full Text** | **Free Full Text** | **F1000 Recommendation**

33. **F** Scharenberg MA, Pippenger BE, Sack R, *et al.*: **TGF-β-induced differentiation into myofibroblasts involves specific regulation of two MKL1 isoforms.** *J Cell Sci.* 2014; **127**(Pt 5): 1079–91.
    PubMed Abstract | **Publisher Full Text** | **F1000 Recommendation**

34. **F** Zhou Y, Huang X, Hecker L, *et al.*: **Inhibition of mechanosensitive signaling in myofibroblasts ameliorates experimental pulmonary fibrosis.** *J Clin Invest.* 2013; **123**(3): 1096–108.
    PubMed Abstract | **Publisher Full Text** | **Free Full Text** | **F1000 Recommendation**

35. **F** Small EM, Thatcher JE, Sutherland LB, *et al.*: **Myocardin-related transcription factor-a controls myofibroblast activation and fibrosis in response to myocardial infarction.** *Circ Res.* 2010; **107**(2): 294–304.
    PubMed Abstract | **Publisher Full Text** | **Free Full Text** | **F1000 Recommendation**

36. **F** Luchsinger LL, Patenaude CA, Smith BD, *et al.*: **Myocardin-related transcription factor-A complexes activate type I collagen expression in lung fibroblasts.** *J Biol Chem.* 2011; **286**(51): 44116–25.
    PubMed Abstract | **Publisher Full Text** | **Free Full Text** | **F1000 Recommendation**

37. **F** Haak AJ, Tsou PS, Amin MA, *et al.*: **Targeting the myofibroblast genetic switch: inhibitors of myocardin-related transcription factor/serum response factor-regulated gene transcription prevent fibrosis in a murine model of skin injury.** *J Pharmacol Exp Ther.* 2014; **349**(3): 480–6.
    PubMed Abstract | **Publisher Full Text** | **Free Full Text** | **F1000 Recommendation**

38. **F** Johnson LA, Rodansky ES, Haak AJ, *et al.*: **Novel Rho/MRTF/SRF inhibitors block matrix-stiffness and TGF-β-induced fibrogenesis in human colonic myofibroblasts.** *Inflamm Bowel Dis.* 2014; **20**(1): 154–65.
    PubMed Abstract | **Publisher Full Text** | **F1000 Recommendation**

39. Halder G, Dupont S, Piccolo S: **Transduction of mechanical and cytoskeletal cues by YAP and TAZ.** *Nat Rev Mol Cell Biol.* 2012; **13**(9): 591–600.
    PubMed Abstract | **Publisher Full Text**

40. Talele NP, Fradette J, Davies JE, *et al.*: **Expression of α-Smooth Muscle Actin Determines the Fate of Mesenchymal Stromal Cells.** *Stem Cell Reports.* 2015; **4**(6): 1016–30.
    PubMed Abstract | **Publisher Full Text** | **Free Full Text**

41. **F** Calvo F, Ege N, Grande-Garcia A, *et al.*: **Mechanotransduction and YAP-dependent matrix remodelling is required for the generation and maintenance of cancer-associated fibroblasts.** *Nat Cell Biol.* 2013; **15**(6): 637–46.
    PubMed Abstract | **Publisher Full Text** | **F1000 Recommendation**

42. **F** Liu F, Lagares D, Choi KM, *et al.*: **Mechanosignaling through YAP and TAZ drives fibroblast activation and fibrosis.** *Am J Physiol Lung Cell Mol Physiol.*

2015; **308**(4): L344–57.
PubMed Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation

43. Speight P, Nakano H, Kelley TJ, *et al.*: **Differential topical susceptibility to TGFβ in intact and injured regions of the epithelium: key role in myofibroblast transition.** *Mol Biol Cell.* 2013; **24**(21): 3326–36.
PubMed Abstract | Publisher Full Text | Free Full Text

44. Piersma B, de Rond S, Werker PM, *et al.*: **YAP1 Is a Driver of Myofibroblast Differentiation in Normal and Diseased Fibroblasts.** *Am J Pathol.* 2015; **185**(12): 3326–37.
PubMed Abstract | Publisher Full Text

45. F Driskell RR, Lichtenberger BM, Hoste E, *et al.*: **Distinct fibroblast lineages determine dermal architecture in skin development and repair.** *Nature.* 2013; **504**(7479): 277–81.
PubMed Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation

46. F Rinkevich Y, Walmsley GG, Hu MS, *et al.*: **Skin fibrosis. Identification and isolation of a dermal lineage with intrinsic fibrogenic potential.** *Science.* 2015; **348**(6232): aaa2151.
PubMed Abstract | Publisher Full Text | F1000 Recommendation

47. F Moore-Morris T, Guimarães-Camboa N, Banerjee I, *et al.*: **Resident fibroblast lineages mediate pressure overload-induced cardiac fibrosis.** *J Clin Invest.* 2014; **124**(7): 2921–34.
PubMed Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation

48. F Marangoni RG, Korman BD, Wei J, *et al.*: **Myofibroblasts in murine cutaneous fibrosis originate from adiponectin-positive intradermal progenitors.** *Arthritis Rheumatol.* 2015; **67**(4): 1062–73.
PubMed Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation

49. Hao H, Gabbiani G, Camenzind E, *et al.*: **Phenotypic modulation of intima and media smooth muscle cells in fatal cases of coronary artery lesion.** *Arterioscler Thromb Vasc Biol.* 2006; **26**(2): 326–32.
PubMed Abstract | Publisher Full Text

50. Hinz B: **Myofibroblasts.** *Exp Eye Res.* 2016; **142**: 56–70.
PubMed Abstract | Publisher Full Text

51. F Torricelli AA, Santhanam A, Wu J, *et al.*: **The corneal fibrosis response to epithelial-stromal injury.** *Exp Eye Res.* 2016; **142**: 110–8.
PubMed Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation

52. F Friedman SL: **Evolving challenges in hepatic fibrosis.** *Nat Rev Gastroenterol Hepatol.* 2010; **7**(8): 425–36.
PubMed Abstract | Publisher Full Text | F1000 Recommendation

53. F Kramann R, Schneider RK, DiRocco DP, *et al.*: **Perivascular Gli1+ progenitors are key contributors to injury-induced organ fibrosis.** *Cell Stem Cell.* 2015; **16**(1): 51–66.
PubMed Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation

54. F Greenhalgh SN, Iredale JP, Henderson NC: **Origins of fibrosis: pericytes take centre stage.** *F1000Prime Rep.* 2013; **5**: 37.
PubMed Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation

55. F Duffield JS: **Cellular and molecular mechanisms in kidney fibrosis.** *J Clin Invest.* 2014; **124**(6): 2299–306.
PubMed Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation

56. Zeisberg M, Kalluri R: **The role of epithelial-to-mesenchymal transition in renal fibrosis.** *J Mol Med (Berl).* 2004; **82**(3): 175–81.
PubMed Abstract | Publisher Full Text

57. F Kim KK, Kugler MC, Wolters PJ, *et al.*: **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**(35): 13180–5.
PubMed Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation

58. Ho WT, Chang JS, Su CC, *et al.*: **Inhibition of matrix metalloproteinase activity reverses corneal endothelial-mesenchymal transition.** *Am J Pathol.* 2015;

185(8): 2158–67.
PubMed Abstract | Publisher Full Text

59. F Galligan CL, Fish EN: **The role of circulating fibrocytes in inflammation and autoimmunity.** *J Leukoc Biol.* 2013; **93**(1): 45–50.
PubMed Abstract | Publisher Full Text | F1000 Recommendation

60. F Reilkoff RA, Bucala R, Herzog EL: **Fibrocytes: emerging effector cells in chronic inflammation.** *Nat Rev Immunol.* 2011; **11**(6): 427–35.
PubMed Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation

61. F Barbosa FL, Chaurasia SS, Cutler A, *et al.*: **Corneal myofibroblast generation from bone marrow-derived cells.** *Exp Eye Res.* 2010; **91**(1): 92–6.
PubMed Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation

62. F Direkze NC, Hodivala-Dilke K, Jeffery R, *et al.*: **Bone marrow contribution to tumor-associated myofibroblasts and fibroblasts.** *Cancer Res.* 2004; **64**(23): 8492–5.
PubMed Abstract | Publisher Full Text | F1000 Recommendation

63. F Behfar A, Crespo-Diaz R, Terzic A, *et al.*: **Cell therapy for cardiac repair--lessons from clinical trials.** *Nat Rev Cardiol.* 2014; **11**(4): 232–46.
PubMed Abstract | Publisher Full Text | F1000 Recommendation

64. F Bianco P, Cao X, Frenette PS, *et al.*: **The meaning, the sense and the significance: translating the science of mesenchymal stem cells into medicine.** *Nat Med.* 2013; **19**(1): 35–42.
PubMed Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation

65. Hinz B: **The myofibroblast in connective tissue repair and regeneration.** In: *Regenerative Medicine and Biomaterials for the Repair of Connective Tissues*: Elsevier; 2010; 39–80.
Publisher Full Text

66. Friedman SL, Sheppard D, Duffield JS, *et al.*: **Therapy for fibrotic diseases: nearing the starting line.** *Sci Transl Med.* 2013; **5**(167): 167sr1.
PubMed Abstract | Publisher Full Text

67. F Muro AF, Moretti FA, Moore BB, *et al.*: **An essential role for fibronectin extra type III domain A in pulmonary fibrosis.** *Am J Respir Crit Care Med.* 2008; **177**(6): 638–45.
PubMed Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation

68. Chaponnier C, Goethals M, Janmey PA, *et al.*: **The specific NH2-terminal sequence Ac-EEED of alpha-smooth muscle actin plays a role in polymerization *in vitro* and *in vivo*.** *J Cell Biol.* 1995; **130**(4): 887–95.
PubMed Abstract | Publisher Full Text | Free Full Text

69. F Hinz B, Gabbiani G, Chaponnier C: **The NH2-terminal peptide of alpha-smooth muscle actin inhibits force generation by the myofibroblast *in vitro* and *in vivo*.** *J Cell Biol.* 2002; **157**(4): 657–63.
PubMed Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation

70. Prunotto M, Bruschi M, Gunning P, *et al.*: **Stable incorporation of α-smooth muscle actin into stress fibers is dependent on specific tropomyosin isoforms.** *Cytoskeleton (Hoboken).* 2015; **72**(6): 257–67.
PubMed Abstract | Publisher Full Text

71. Gunning PW, Hardeman EC, Lappalainen P, *et al.*: **Tropomyosin - master regulator of actin filament function in the cytoskeleton.** *J Cell Sci.* 2015; **128**(16): 2965–74.
PubMed Abstract | Publisher Full Text

72. Reed NI, Jo H, Chen C, *et al.*: **The $\alpha_v\beta_1$ integrin plays a critical *in vivo* role in tissue fibrosis.** *Sci Transl Med.* 2015; **7**(288): 288ra79.
PubMed Abstract | Publisher Full Text | Free Full Text

73. F Henderson NC, Arnold TD, Katamura Y, *et al.*: **Targeting of α_v integrin identifies a core molecular pathway that regulates fibrosis in several organs.** *Nat Med.* 2013; **19**(12): 1617–24.
PubMed Abstract | Publisher Full Text | Free Full Text | F1000 Recommendation

74. F Santhiago MR, Netto MV, Wilson SE: **Mitomycin C: biological effects and use in refractive surgery.** *Cornea.* 2012; **31**(3): 311–21.
PubMed Abstract | Publisher Full Text | F1000 Recommendation

Open Peer Review

Current Referee Status: ☑ ☑

Editorial Note on the Review Process

F1000 Faculty Reviews are commissioned from members of the prestigious F1000 Faculty and are edited as a service to readers. In order to make these reviews as comprehensive and accessible as possible, the referees provide input before publication and only the final, revised version is published. The referees who approved the final version are listed with their names and affiliations but without their reports on earlier versions (any comments will already have been addressed in the published version).

The referees who approved this article are:

Version 1

1   **Steven E. Wilson**, Cole Eye Institute, Cleveland Clinic, Cleveland, OH, USA
    Competing Interests: No competing interests were disclosed.

2   **Jack Gauldie**, Department of Pathology and Molecular Medicine, McMaster University, Hamilton, Ontario, Canada
    Competing Interests: No competing interests were disclosed.