

Myofibroblast-Mediated Contraction

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ABSTRACT

Myofibroblast-mediated contraction is viewed as a cycle of four steps. The first step is stimulation of myofibroblasts by lysophospholipids leading to the activation of G proteins and ending with contraction of the actin-myosin complex. The next step is the transmission of the intracellular contractile force at the focal adhesions of myofibroblasts; a step that involves talin, vinculin, paxillin, Hic-5, and the integrin receptors. In the third step, fibronectin will act as the extracellular link between the integrin receptors and the extracellular collagen. Finally, "sensing" tension and the maintenance of myofibroblast activity represent the fourth step. The clinical relevance of each step is then discussed in the form of modalities to prevent excessive scarring/fibrosis.

Key Words: *Myofibroblast. Contraction. Fibrosis. Wound healing.*

INTRODUCTION

Wounding results in the expression of myofibroblasts: There are multiple sources of wound myofibroblasts.¹ The first and most important source is the transformation of the normal residing dermal fibroblasts into proto-myofibroblasts and then into myofibroblasts. Myofibroblast differentiation is mediated by several factors and cytokines but transforming growth factor β 1 (TGF β 1) remains the most important mediator.²⁻⁴ TGF β 1 stimulates TGF β receptors leading to the activation of Smad 3. Smad 3 makes a complex with Smad 4 and enters into nucleus to activate gene synthesis of collagen, α -smooth muscle actin (α SMA), and fibronectin with alternatively spliced segments known as EDA and EDB. Other sources of wound myofibroblasts include circulating fibrocytes (which arise from the bone marrow), pericytes (perivascular cells), and smooth muscle cells of the dermal blood vessels.¹

In primary wound healing, myofibroblasts have several functions such as collagen deposition and mediation of the 'cross-talk' within the extracellular matrix. After two weeks, myofibroblasts undergo apoptosis in wounds healing by primary intention.¹⁻⁵ In wounds healing by secondary intention, myofibroblasts persist in the granulation tissue to mediate skin wound contraction. Recent scientific research has detailed every step of wound contraction. The main problem is the fact that the information written on these steps is mostly written in depth by basic science researchers; and this makes it

hard for clinicians to follow. The aim of this article is to present these steps in a simplified way for clinicians, to provide ample illustrations to aid the understanding of these steps, and finally to explore their clinical relevance.

Literature search strategy: The search was done using PubMed database. Two keywords were used: "Myofibroblast" and "Contraction" with no time bar. A total of 768 articles were scanned. The articles were mainly describing the basic science of a particular event of myofibroblast contraction or describing the therapeutic potential of a medication to treat excessive scarring. The basic science of myofibroblast-mediated contraction was categorised into four simplified steps for the clinicians, followed by therapeutic implications of each step.

Step I: Stimulation of myofibroblasts by lysophosphatidic acid (LPA) and sphingosine-1-phosphate (S1P): The initial step of myofibroblast contraction is the stimulation of myofibroblasts by S1P and LPA. S1P and LPA are lysophospholipids (derived from cell membrane components) which are released mainly from activated platelets.⁶ There are specific receptors for S1P and LPA in the cell membrane of myofibroblasts. All of these receptors are G-protein coupled receptors, which result in the activation of G-proteins. Activation of G12/13 proteins results in the activation of RhoA (a small GTPase). The end result is phosphorylation of myosin light chain and contraction of the actin-myosin complex. This contraction is persistent and is known as "stressed matrix" contraction.⁶

The same receptor againsts (LPA and S1P) also activate Gq/11 proteins resulting in this activation of phospholipase C and hydrolysis of inositol triphosphate. The end result is an increase in the intracellular free calcium. The calcium-calmodulin complex will then mediate the activation of myosin light chain kinase which, in turn, phosphorylates the myosin light chain.

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The resulting actin-myosin contraction is rapid and transient and not persistent.⁷ A summary of these events is shown in Figure 1.

Step II: The transmission of the intracellular contractile force at mature and super mature focal adhesions: Contraction of the stressed matrix has to be efficiently transmitted at areas known as focal adhesions, in the cell membrane of myofibroblasts. These focal adhesions act like receptors and are made up of complexes of several molecules including integrins, kinases, paxillin, Hic-5 (hydrogen peroxide inducible clone-5), talin, and vinculin. It is important to note that focal adhesions are not only the site of transmission of the intracellular contractile force to the extracellular matrix, but they are also the sites through which myofibroblasts can “sense” tension in the extracellular matrix. The most important focal adhesion receptors are the $\alpha 5\beta 1$ receptors.¹⁻⁵

Talin and vinculin are cytoskeletal proteins for the mediation of transmission of contractile forces at focal adhesions.⁸ Talin is composed of three domains, while vinculin is composed of two domains (Figure 2). As seen in Figure 2, the talin-vinculin complex connects the intracellular actin filaments to the integrin receptors at focal adhesions. “Single molecule fluorescence force spectroscopy” can be used to measure tension across vinculin. Grashoff *et al.* showed that the tension across vinculin is about 2.5 pN (Pico Newton) in stable (immature) focal adhesions, but is much higher in mature adhesions.⁹ Paxillin and Hic-5 are closely related, act as scaffolds for signalling at the focal adhesions, and are both associated with vinculin. The interaction of Paxillin and Hic-5 with vinculin is differentially regulated by Rac1 and RhoA.¹⁰ Hence, one may consider vinculin as a regulator of focal adhesion dynamics.

Step III: Fibronectin as the extracellular link between integrin receptors and the extracellular collagen: Fibronectin (Figure 3) is a dimer containing two similar subunits linked covalently by two disulfide bonds. Fibronectin is made up of three types of amino acid repeats. These repeats are termed type I, II, and III repeats. Fibronectin is encoded by a single gene and it undergoes several patterns of alternative splicing, giving rise to about 20 possible types of cellular fibronectin. As seen in Figure 3, splicing occurs within type III amino-acid repeats and includes the EDA (extra-domain A), EDB (extra-domain B) and the variable or connecting segment III (CS-III).¹¹ EDA and B variants are prominent in conditions of excessive fibrosis.

Relevant to the current review are the RGD and PHSRN cell-binding domains of fibronectin. Each letter of these cell-binding domains refers to an amino acid. Hence, RGD refers to “Arg-Gly-Asp” amino acid sequence, and PHSRN refers to “Pro-His-Ser-Arg-Asn” amino acid

sequence. These relatively short sequences are the sites of attachment of fibronectin to the $\alpha 5\beta 1$ integrins at focal adhesions.^{11,12} The fibronectin molecule also has collagen-binding domains (composed of type I and II repeats) which will bind to collagen of the extracellular matrix.^{11,12} Hence, fibronectin will act as the extracellular link between focal adhesion receptors and collagen; as opposed to the talin-vinculin complex, which acts as the intracellular link between the focal adhesion receptors and actin. In other words, these two links will act to translate the intracellular actin-myosin contraction into an extracellular matrix contraction (Figure 4).

It is important to realize that fibronectin-fibronectin association also occurs resulting in fibril formation in a process called “fibrillogenesis” (Figure 5).¹³ This is a cell-mediated matrix assembly process in which actin contraction linked at the $\alpha 5\beta 1$ receptors is translated to fibronectin molecules. This will result in exposure of binding sites within the fibronectin molecules leading to the addition of more fibronectin molecules, leading to the assembly of fibronectin fibrils (Figure 5).

Step IV: “Sensing” tension and the maintenance of myofibroblasts: Myofibroblasts “sense” tension of the extracellular matrix through the super-mature focal adhesions. This occurs through the activity of several compounds including paxillin, Hic-5, talin, vinculin, and fibronectin fibrils as well as integrin receptor configuration.¹⁻³ The increased stiffness of the extracellular matrix along with other cytokines and TGF β 1 will induce (via Rho kinase) the polymerization of G-actin into F-actin (Figure 6). This will result in the release of MRTFA (myocardin-related transcription factor-A). MRTFA translocates to the nucleus where it makes a complex with SRF (serum response factor), leading to the induction of gene synthesis of proteins important for the persistence of myofibroblasts. The maintenance of this vicious circle requires Hic-5, TGF β 1, spliced fibronectin EDA and B, and connective tissue factor (also known as CCN2).^{14,15}

Clinical relevance: Myofibroblast activity and contraction may be viewed as “beneficial” in wound healing by secondary intention as well as in the healing of tendon, ligament, and bone. However, abnormal myofibroblast activity and contraction is seen in many pathological processes such as hypertrophic scars, Dupuytren contracture, scleroderma, multiple sclerosis, and organ fibrosis in the lung, heart, liver and kidney. A detailed knowledge of myofibroblast-mediated contraction will help develop methods and drugs to overcome excessive myofibroblast activity.

Therapeutic drugs/modalities that target Step I: FTY720, BMS-986020, ROCK inhibitors: There are many promising pharmacological directions in the world of LPA and S1P signalling.¹⁶ Stoddard and Chun recently reviewed compounds that target this signalling.

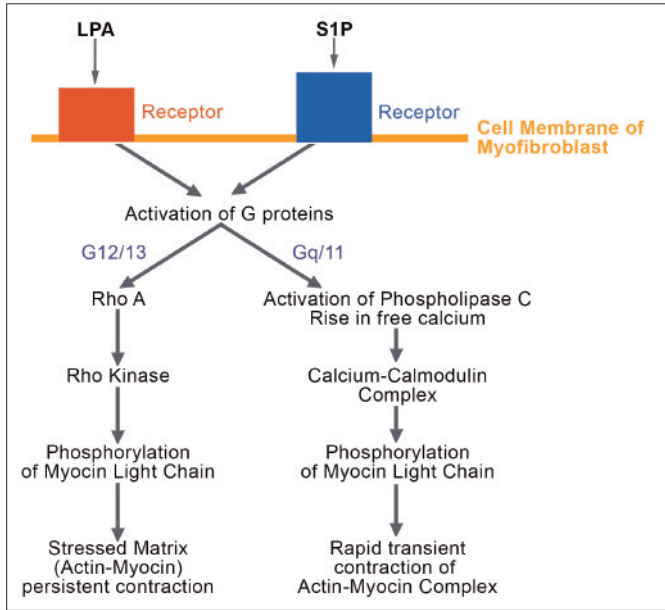


Figure 1: A summary of the events of the first step (see text for details).

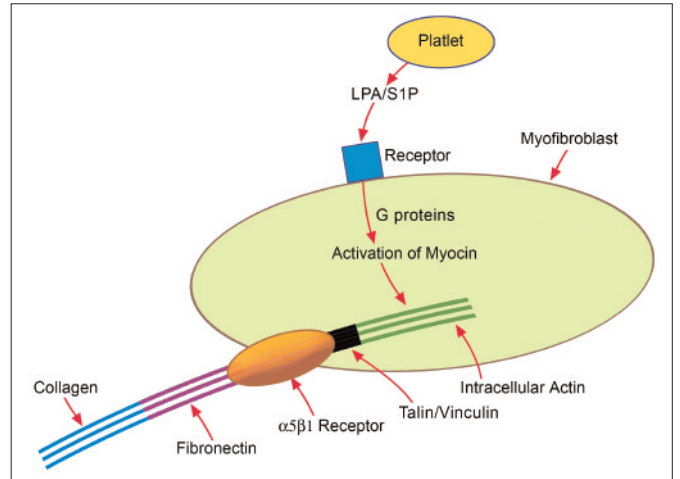


Figure 4: Talin-Vinculin complex is the intracellular link and fibronectin is the extracellular link to translate the intracellular actin-myocin contraction into an extracellular matrix contraction.

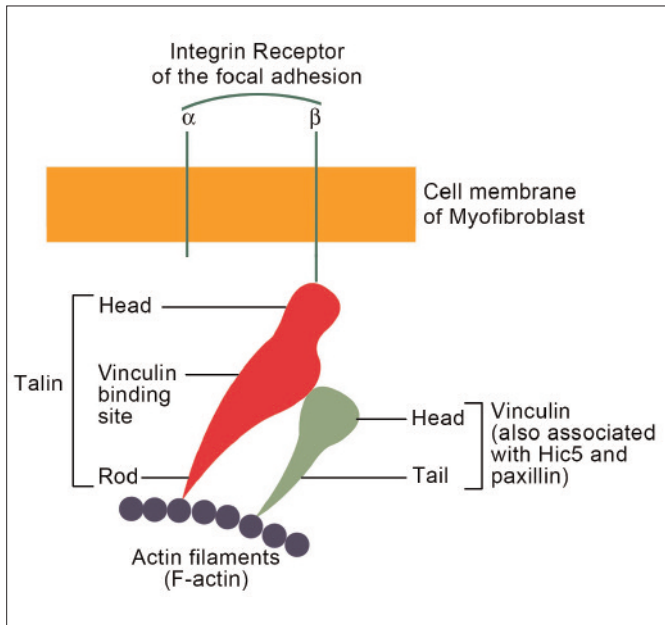


Figure 2: The second step: Talin - Vinculin complex (along with Hic-5 and Paxillin) act as a link between the contracting actin-filaments and integrin receptors at the focal adhesions of myofibroblasts.

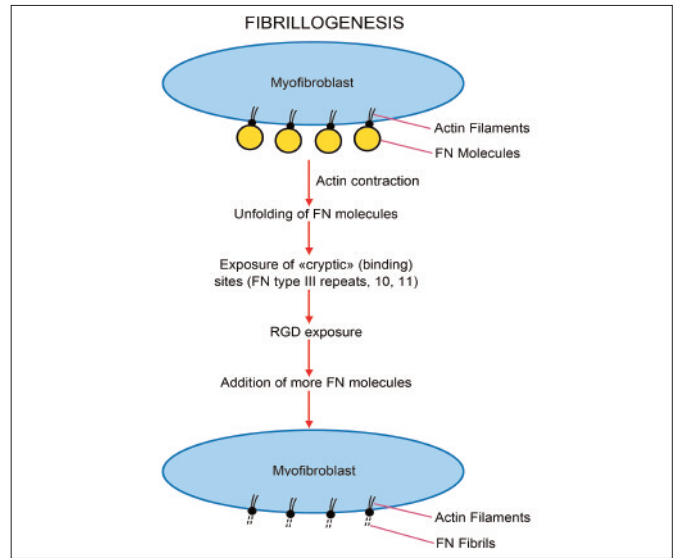


Figure 5: The process of fibrillogenesis (see text for details) (FN=fibronectin).

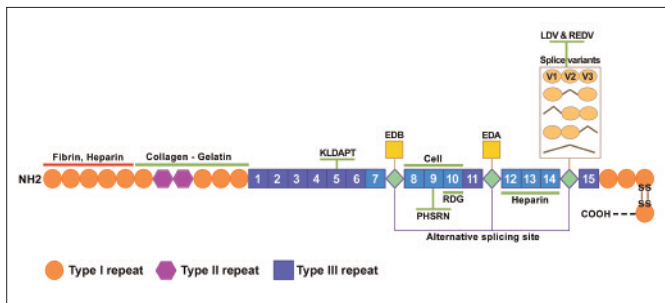


Figure 3: The structure of fibronectin. The EDA and B (Extra Domain A and B) induce myofibroblast activation. The cell binding domains (RGD and PHSRN) bind fibronectin to the $\alpha 5 \beta 1$ integrins at focal adhesions.

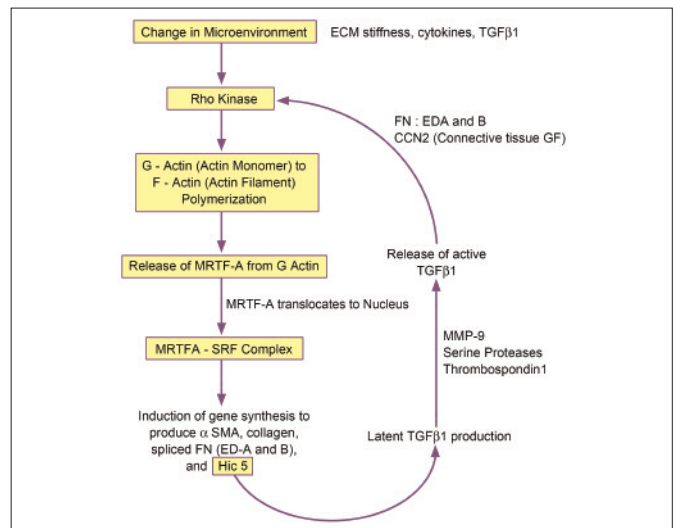


Figure 6: The vicious circle of sensing tension-persistence of myofibroblasts (see text for details). (FN= Fibronectin, EDA and B = Extra Domain A and B, MRTF-A= Myocardin Related Transcription Factor A, SRF= Serum Response Factor).

Although most of these compounds are still in the “pre-clinical” stage, some are FDA approved and some have completed phase II trials. FTY720 targets S1P and is FDA approved for multiple sclerosis.¹⁶ Another example is BMS-986020, which targets LPA and has completed phase II trials for idiopathic pulmonary fibrosis. ROCK inhibitors may also be used to reduce myofibroblast contraction;¹⁷ and they are under clinical assessment for cardiovascular diseases.¹⁸

Therapeutic drugs/modalities that target Step II: c.No.SC-37685 SiRNA, CX-4945, Pyrimidine-FAK inhibitor, Adiponectin, ADP355: Knocking down Hic-5 leads to loss of mature focal adhesions and reduces myofibroblast contraction; and this may have a role in managing hypertrophic scars.^{15,19} Small interfering RNAs directed against the human Hic-5 sequence (c.No.SC-37685) is currently available and is known to suppress fibrosis.¹⁹

The role of paxillin and Hic-5 goes beyond contraction and migration of myofibroblasts in wounds and pathological scarring. Deakin and Turner demonstrated the distinct roles for paxillin and Hic-5 in regulating cancer invasion and metastasis.²⁰ Focal adhesion kinase (FAK) is induced by TGF β and interacts with paxillin to regulate actin cytoskeleton formation as well as cancer cell invasion.²⁰ Inhibition of FAK-paxillin activation is possible by the casein kinase-2 inhibitor: CX-4945. Hence, CX-4945 is a drug candidate against cancer cell metastasis.²⁰

Myofibroblasts are the major cells in the development of interstitial fibrosis of renal transplants. Targeting vinculin-paxillin adhesion complexes may prove useful to prevent chronic dysfunction of renal allografts.²²

Targeting FAK will also reduce myofibroblast contractility. FAK phosphorylation inhibitors have potential use in scleroderma.²³ The agent 4-amino-5-(4-chlorophenyl)-7-(butyl)pyrazolo[3,4-d]pyrimidine, which is an inhibitor of FAK, markedly diminishes SMA expression in scleroderma fibroblasts.²³

In vitro, adiponectin induces de-phosphorylation of FAK. *In vivo* experiments also showed that adiponectin modulates focal adhesion disassembly in activated hepatic stellate cells and this has implications in the management of hepatic fibrosis.²³ However, the therapeutic use of adiponectin is limited by its quaternary structure and effective blood concentrations.²⁴ Hence, a synthetic peptide with adiponectin properties (ADP355) is now available for clinical assessment in liver fibrosis.²⁴

Finally, knowledge of the mechanisms of talin-integrin interactions will help delineate new methods to suppress pathological fibrosis.²⁵

Therapeutic agents/modalities that target Step III: triamcinolone, collagenase, nAG, tranilast: Attenuation of excessive fibrosis may also be done by modulating

fibronectin and collagen, which are the key players of step III.

Collagen levels within the extracellular matrix are controlled by a balance of MMP (matrix metalloproteases) and TIMP (tissue inhibitors of MMP). MMP includes many collagenases and gelatinases. One classic example is the use of triamcinolone injections in hypertrophic scars and nodules of Dupuytren's disease.²⁶ Triamcinolone decreases α 2-macroglobulin, which is a potent inhibitor of collagenase activity. Hence, triamcinolone will indirectly increase the intrinsic collagenase activity. Another example is the use of collagenase as a non-surgical modality of Dupuytren's cords.²⁷

There are numerous experimental drugs that suppress collagen synthesis. A review of these experiments is beyond the scope of this article, but one interesting protein called nAG was recently shown to have a very strong suppressive effect on collagen I and III synthesis. Furthermore, the nAG protein will enhance collagen degradation and decrease fibroblast proliferation.²⁸

The lack of neural regeneration after spinal cord injury is attributed to glial and fibrotic scars. Agents (such as tranilast) that suppress fibronectin at the site of cord injury improve neural regeneration.²⁹ Targeting fibronectin may be tricky because fibronectin is also required for epithelialization.³⁰ Keratinocytes have α 5 β 1 receptors which interact with fibronectin, activating keratinocyte migration.³¹ An example is the healing process following keratectomy for corneal disease. Enhancing corneal fibronectin deposition will promote corneal epithelialization.³² However, reducing corneal fibronectin deposition is desired to prevent excessive corneal fibrosis.³³

Therapeutic drugs/modalities that target Step IV: SiRNA against TGF β 1, decorin, topical CCN1, CCG-203971: Since TGF β 1 is the major factor in the maintenance of myofibroblasts, anti-TGF β 1 modalities seem a reasonable option to prevent excessive scarring or fibrosis. One example of such modalities is the inhibition of TGF β receptor I gene expression using SiRNA (small interfering RNA).³⁴

Decorin is a small leucine-rich proteoglycan which interacts with collagen in the extracellular matrix and acts to transmit mechanical signals. It also interacts with TGF β 1 reducing its activity. Therefore, reduction of the normal decorin levels will result in scar hypertrophy³⁵ and organ fibrosis.³⁶ Hence, prevention of excessive fibrosis/scarring may be obtained through the delivery of decorin to the wound.³⁷

Another method of attacking myofibroblasts in Step IV is to promote their apoptosis. The main inducer of myofibroblast apoptosis is Cyr61 (Cysteine Rich Angiogenic Inducer 61), which is also known as CCN1.

Hence, increasing the levels of CCN1 in the wound (such as by using topical purified CCN1) is an emerging therapeutic target against excessive fibrosis.³⁸ It is important to note that the second member of the CCN family (CCN2) is the connective tissue growth factor which promotes the persistence of myofibroblasts. Hence, reducing the levels of CCN2 is desirable in the management of excessive fibrosis.³⁸

Finally, MRTFA and SRF are two key players of myofibroblast persistence (Figure 6). Hence, inhibitors of MRTFA-SRF regulated gene transcription will prevent excessive fibrosis.³⁹ A novel small-molecule inhibitor of MRTF/SRF (CCG-203971) is now available and can provide a new approach to therapy for systemic sclerosis.³⁹

However, one should not forget that several biofeedback loops exist, which could result in a paradoxical effect. For example, severe suppression of collagen III will result in a biofeedback loop resulting in an increase in TGF β 1 and an increase in myofibroblast expression.⁴⁰ This may explain the paradoxical clinical features of patients with Ehlers-Danlos syndrome type IV. These patients have a mutation in the *COL3A1* gene resulting in reduced amount of collagen III in the skin, arteries and intestine. These patients are known to develop visceral rupture and aneurysms and yet they also develop spontaneous multiple keloids.⁴¹ The same paradoxical effect may be seen clinically following the injection of collagenase to breakdown collagen within the cords of Dupuytren's disease. The collagenase may reduce the collagen content of the cord to a level that will induce myofibroblast expression leading to the complication of deep tissue scarring of the palm at the site injection.⁴²

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