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The myofibroblast matrix: implications for tissue repair and fibrosis

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Abstract

Myofibroblasts, and the extracellular matrix (ECM) in which they reside, are critical components of wound healing and fibrosis. The ECM, traditionally viewed as the structural elements within which cells reside, is actually a functional tissue whose components possess not only scaffolding characteristics, but also growth factor, mitogenic, and other bioactive properties. Although it has been suggested that tissue fibrosis simply reflects an 'exuberant' wound-healing response, examination of the ECM and the roles of myofibroblasts during fibrogenesis instead suggest that the organism may be attempting to recapitulate developmental programmes designed to regenerate functional tissue. Evidence of this is provided by the temporospatial re-emergence of embryonic ECM proteins by fibroblasts and myofibroblasts that induce cellular programmatic responses intended to produce a functional tissue. In the setting of wound healing (or physiological fibrosis), this occurs in a highly regulated and exquisitely choreographed fashion which results in cessation of haemorrhage, restoration of barrier integrity, and re-establishment of tissue function. However, pathological tissue fibrosis, which oftentimes causes organ dysfunction and significant morbidity or mortality, likely results from dysregulation of normal wound-healing processes or abnormalities of the process itself. This review will focus on the myofibroblast ECM and its role in both physiological and pathological fibrosis, and will discuss the potential for therapeutically targeting ECM proteins for treatment of fibrotic disorders.

Keywords

ECM; myofibroblast; fibrosis

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Author contribution statement

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Introduction

Myofibroblast activation is a key event in physiological and pathological tissue repair. Myofibroblasts are the primary extracellular matrix (ECM)-secreting cells during wound healing and fibrosis, and are largely responsible for the contractility of scar tissue as it matures [1,2]. The contribution of myofibroblasts and their elaborated ECM to normal and pathological tissue repair [3] has been well studied in the lung [4–6], liver [7–9], kidney [10,11], skeletal muscle [12], systemic sclerosis [13–15], heart [16–18], and the stromal reaction to tumours [19,20].

A number of recent reviews have considered the nature of myofibroblast progenitors in different organs [21], including resident fibroblasts [3,19,22–25], fibrocytes [26–28], smooth muscle cells [29], pericytes [30–33], epithelial and endothelial cells undergoing endothelial (EndoMT) or epithelial-to-mesenchymal transition (EMT) [34–38], mesenchymal stromal cells [39,40], and hepatic stellate cells [23], to name only the most prominent. Others have focused on the chemical and mechanical conditions controlling myofibroblast formation and survival [41], functional and phenotypic characteristics [42,43], and their suitability as therapeutic targets [44–48]. Due to space constraints, these concepts will not be explored here.

Despite the abundant literature concerning the myofibroblast, surprisingly little focuses on specific features and functions of the myofibroblast ECM. Indeed, disturbance of the ECM and remodelling by myofibroblasts has a profound impact on their own behaviour and that of other cell types sharing the same microenvironment. This is intuitive since the ECM performs a multitude of biological functions, including providing mechanical stability, protection, and guidance for cells [49–51], and acting as a repository for growth factors [52–54].

The myofibroblast: born to produce and remodel ECM

Myofibroblasts were first identified four decades ago as fibroblastic cells that simultaneously exhibit prominent endoplasmic reticulum and contractile microfilament bundles in wound granulation tissue [55]. One prominent feature of the myofibroblast is the neo-expression of α-smooth muscle actin (α-SMA) in stress fibres [56], the molecular basis for their high contractile activity. However, not all α-SMA-expressing cells are myofibroblasts. For example, α-SMA-positive cells that do not form microfilament bundles are not considered myofibroblasts since they are lacking their defining contractile element [57]. Conversely, α-SMA-negative fibroblasts that express microfilament bundles are functional contractile myofibroblasts, at least *in vivo*. Since fibroblasts almost inevitably form microfilament bundles (stress fibres) in standard cell culture conditions, ‘myofibroblast’ denotes α-SMA-positive stress fibre-forming cells.

It bears mentioning that much of our understanding of myofibroblast behaviour arises from *in vitro* studies in which culture conditions vary greatly (eg culturing in ECM-coated dishes, culturing on ‘soft’ agar, culturing in attached or detached collagen gels). This may account for discrepant results among studies and should be considered when interpreting data reported in the literature. One must also recognize that *in vivo*, fibroblasts and

myofibroblasts encounter multiple ECM components simultaneously, thereby potentially altering behaviours from those observed in the experimental setting. Certainly, differences between fibroblast behaviour in two-dimensional and three-dimensional culture conditions are well documented [58] and also inject variability into the results of *in vitro* studies. Finally, the role of mechanotransduction – the sensing of matrix stiffness and response to such stiffness by cells – is beginning to be elucidated in fibroblasts and myofibroblasts, and also adds yet another layer of complexity to our understanding of the myofibroblast ECM. Indeed, a percentage of fibroblasts spontaneously acquire a myofibroblast phenotype in culture [57,59], likely due to stiffness of the culture vessel.

Although collagen I and collagen III are often cited as the primary ECM proteins expressed by myofibroblasts, the myofibroblast produces myriad other ECM proteins during wound repair and fibrosis, such as collagen types IV, V, and VI [60]; glycoproteins; and proteoglycans such as fibronectin, laminin, and tenascin [3,61–72]. It is worth noting, however, that myofibroblasts are not necessarily the only source of these proteins, as epithelial, inflammatory, and endothelial cells may all produce these proteins as well. A schematic of the myofibroblast ECM to be discussed is shown in Figure 1.

Collagens

Collagens are primarily structural proteins composed of three procollagen chains configured in a classic triple helical pattern. Early in the course of wound granulation, myofibroblasts deposit type III collagen. This form imparts a measure of plasticity to the wound in the early phase of healing, although recent data suggest that collagen III deficiency promotes myofibroblast differentiation and wound contraction [73]. When granulation tissue is resorbed following physiological wound repair, myofibroblasts undergo apoptosis (see below) and the more rigid type I collagen is biochemically identified. Under pathological conditions (eg the proliferative cellular phase of palmar fibromatosis or areas of mesenchymal stromal invasion in breast carcinomas), type III collagens appear to be increased [74,75], as are type V collagens in desmoplastic human breast carcinomas and in small airway fibrosis of bronchiolitis obliterans complicating chronic lung transplant rejection [76–78]. Of course, densely fibrotic tissues demonstrate an abundance of type I collagens, but also type VI collagens [79–83].

As wound healing approaches completion, apoptotic gene programmes are expressed within myofibroblasts, resulting in a relatively hypocellular scar. Cytokines that stimulate ECM synthesis early on are repressed once wound closure is completed and a functional basement membrane has been synthesized, thus suggesting the existence of a feedback loop [84]. However, in pathological fibrosis, evidence suggests that failure to initiate apoptosis of myofibroblasts (or decreased sensitivity to apoptotic stimuli) accounts for the seeming persistence of these cells in fibrotic tissues.

Fibronectins (FNs)

FN is expressed by multiple cell types and plays a key role in cell adhesive and migratory behaviour [85,86]. The functional FN dimer consists of two similar or identical subunits of 220–250 kDa that are held together by two disulphide bonds near their carboxyl-termini.

Like many glycoproteins, each monomer consists of a combination of different types of homologous repeating domains; in the case of FN, there are three, termed types I, II, and III. However, by virtue of alternative splicing of the pre-mRNA, two extra type III repeats (termed EDA for extra domain A and EDB for extra domain B) may be inserted into the mature protein; the splicing of these domains is independent of each other [85,87] but is highly up-regulated by the profibrotic cytokine TGF-β [88]. Alternative splicing of FN is particularly prominent during embryonic development, as well as during wound healing, pathological fibrosis, and malignancy, and gives rise to the term 'oncofetal' ECM. Evidence suggests that alternatively-spliced EDA FN (but not plasma FN) is necessary for TGF-β1-induced myofibroblast differentiation [89,90] and is thus a critical component of the myofibroblast ECM.

As a separate contribution, FN also binds a large number of growth factors that may promote myofibroblast differentiation. Most notably, FN localizes latent TGF-β1 complex by binding latent TGF-β binding proteins (LTBPs, see below) [91]. In addition, FN binds vascular endothelial growth factor (VEGF) [92], bone morphogenetic protein (BMP) 1 [93], hepatocyte growth factor (HGF) [94], fibroblast growth factor (FGF)-2 [95], and platelet-derived growth factor (PDGF) [96], all of which may contribute to the myofibroblast phenotype.

Elastin

Elastin, a major ECM protein involved in connective tissue homeostasis, provides organs with structural integrity and is responsible for absorption of mechanical overload preventing damage [97]. Smooth muscle cells and fibroblasts are the major elastin-producing cells in normal tissues [98] such as skin, heart, arteries, and lung, which all undergo cyclic mechanical loading and unloading throughout life. Elastin deposition and organization occurs mainly during the late fetal and early neonatal periods and is reduced during maturity to a low turnover rate [99].

It has been generally understood that elastin production by fibroblasts is low or absent following injury, which partly accounts for the reduced elasticity and breaking strength of scar tissue compared with the intact connective tissue [52]. Because of the low elastin turnover in normal and injured skin and arteries, current strategies aim to supply elastin-like proteins either by grafting [100–102] or by stimulating cellular elastin production [103,104]. However, some studies have shown that elastin production by fibroblasts is quite elevated after tissue damage in response to a number of cytokines, such as TNF-α, IL-1β, and TGF-β1 [105,106]. For example, in constrictive bronchiolitis obliterans, characterized by fibrosis development in the small airways, α-SMA-positive myofibroblasts demonstrated enhanced elastin expression [107].

Fibrillins and LTBPs

In addition to the major fibrillar components, the myofibroblast ECM contains a microfibrillar network formed by members of the fibrillin and latent TGF-β binding protein (LTBP) family. In humans, these glycoprotein families consist of three homologous fibrillin isoforms (fibrillin-1, -2, and -3) and four LTBPs (LTBP-1, -2, -3, and -4) that are mainly

characterized by highly repetitive and disulphide-rich domains. Microfibrils provide the basis for tropoelastin binding during elastic fibre formation, enhance the structural integrity of tissues and organs, and target growth factors such as TGF-β and bone morphogenic protein (BMP) to the ECM [108–110]. The disruption of microfibrillar assembly or growth factor association with fibrillins due to mutations within fibrillin genes leads to clinical relevant pathological connective tissue conditions such as Marfan's syndrome, congenital contractual arachnodactyly, and systemic scleroderma [111–115].

LTBPs share similarities with fibrillins in their repetitive sequence and domain structure. However, LTBPs are considerably smaller, ranging from 125 to 160 kDa when compared with fibrillins (~350 kDa). Analysis of LTBP isoforms from cultured human hepatic myofibroblast ECM reveals all four isotypes, suggesting that these proteins may play a role in liver fibrosis [116]. Moreover, culture studies may give an insight into the sequence of events in ECM assembly by fibroblasts during embryogenesis and tissue repair. Recent mouse fibrillin-1 knock-out studies showed that LTBP-1 incorporation into the ECM of fibroblasts depends on a FN network compared with the ECM association of LTBP-3 and LTBP-4, which depends on fibrillin-1 microfibrils [117]. In fibroblasts that are missing the gene for FN, LTBP-1 fails to incorporate into the ECM in the early phase but can be assembled in later stages [118].

LTBP-1 is crucial for tissue repair, fibrosis, and myofibroblast biology because it serves as a storage protein for TGF-β1. The TGF-β family comprises multipotent cytokines modulating cell growth, apoptosis, inflammation, and ECM synthesis. In mammals, these functions are mediated by the widely expressed three isoforms TGF-β1, TGF-β2, and TGF-β3 that are encoded by three different genes of high homology [119]. TGF-β1 appears to be the most prevalent isoform that associates with fibroblast-to-myofibroblast activation [120], although both of the other isoforms have also been demonstrated to perform this action *in vitro* [121]. *In vivo*, TGF-β3 appears to attain a myofibroblast-supressing role [121,122]. LTBP-1 regulates the bioactivity of TGF-β1 at multiple levels: (1) it promotes efficient latent TGF-β1 secretion by assembling the large latent complex [123]; (2) it targets latent TGF-β1 as a large latent complex to the ECM by interacting with different proteins including FN and fibrillin [109,124,125]; and (3) it controls and directs cell-mediated TGF-β1 activation [125–127].

In addition to the aforementioned, myriad other ECM components can be found in the myofibroblast ECM, including fibulins, matricellular proteins (such as CCN proteins, osteopontin, periostin, and SPARC, to name but a few), tenascins, and thrombospondins. These proteins have all been implicated in fibrogenesis and wound repair to various degrees, with the matricellular protein CCN2 (connective tissue growth factor, CTGF) and tenascin-C perhaps being the best studied. Similarly, experimental data supporting the role of WISP-1, SPARC, osteopontin, and thrombospondins in myofibroblast functions in wound healing and fibrosis have been amply documented [52,128–143]. Below, we will highlight some recent evidence of the roles of these ECM proteins in wound repair and fibrosis.

CCN2 (CTGF)

CCN proteins [so named because of the names of the first three family members identified: cysteine-rich 61 (CYR61), connective tissue growth factor (CTGF), and nephroblastoma overexpressed (NOV) [144]] are integral components of the ECM related to fibrosis and myofibroblast activation. Despite the designation as a growth factor, CCN2 is not a cytokine but an integral ECM protein that exerts its function through binding of cell integrins alone or recruitment of co-receptors [145]. A number of reviews have summarized CCN2 functions in fibrosis [146–148].

Expression of CCN2 (CTGF) is locally up-regulated in a variety of fibrotic conditions and elevated in the serum of subjects with fibrosis. In addition, mutations in the *CCN2* gene promoter are associated with systemic sclerosis in humans [149]. Experimentally, blocking or deleting CCN2 efficiently reduces fibrosis, thus identifying CCN2 as a potential critical modulator of fibrosis. However, subsequent studies seem to suggest that activating functions of CCN2 occur either up- or down-stream of TGF-β1 signalling since simultaneous blocking of TGF-β1 abolished their myofibroblast-activating effect [3,148]. TGF-β1 induces CCN2 expression in a variety of fibroblast culture and animal fibrosis models, nourishing the concept that CCN2 is a mere downstream mediator of TGF-β1 in myofibroblast differentiation [131]. However, different fibroblast culture models demonstrated expression of CCN2 in response to factors other than TGF-β1, such as endothelin-1 [150]. In many organs, however, CCN2 seems to work synergistically with TGF-β1 in enhancing fibrosis but does not induce fibrosis and/or myofibroblast activation in the absence of TGF-β1 or injury [151,152].

Tenascin-C

Tenascin-C is a member of the tenascin family of ECM proteins (which also include tenascins-X, -R, and -W). Tenascin-C is classically regarded as a marker for the immature ECM in the earlier phases of tissue repair, promoting stromal cell population of provisional ECM by generating a migration-supporting adhesive environment and exerting chemokinetic effects [153]. Indeed, tenascin-C plays a role in myofibroblast recruitment [154]. Whereas tenascin-C is down-regulated in normally healing wounds, it persists in hypertrophic scar tissue, where it seems to prevent cell apoptosis and prolongs the ECM synthesis and proliferative phase [153,155]. Tenascin-C null mice are protected against fibrosis in the lung [156] and liver [157] with reduced amounts of α-SMA-positive myofibroblasts. Less is known about the possible implication of other tenascin family members in myofibroblast biology and fibrosis. Tenascin-X knock-out mice exhibit reduced collagen amounts in skin dermis, which shares phenotypic similarities with the human Ehlers–Danlos syndrome, including increased extensibility and reduced strength of the skin [158,159]. Although cutaneous wounds of tenascin-X knock-out mice have reduced breaking strength, the contribution of myofibroblasts to the impaired biomechanical properties of the granulation tissue has not been tested yet [160].

Proteoglycans

Proteoglycans (including heparan sulphate proteoglycans, hyaluronan, syndecans, and small leucine-rich proteoglycans) are critical components of the wound-healing response and are also implicated in tissue fibrosis. Experimental and mechanistic studies implicate these molecules in facilitating the assembly of matrices and the incorporation of growth factors (such as LTBP-1/TGF-β complexes) into the ECM [161].

Hyaluronan has long been associated with conditions of fibrosis, and hyaluronic acid (HA) is clinically used as a serum biomarker for liver fibrosis [162]. In addition, HA is purported to regulate myofibroblast activation and persistence in a TGF-β1-dependent manner [163,164]. The mechanisms of this action are not entirely clear, although fibroblast binding to HA positions the TGF-β1 receptor close to the HA receptor CD44, which affects downstream TGF-β1 signalling [165]. HA also stabilizes cell–ECM adhesions [166], which are crucial for myofibroblast mechanosensing and activation [167]. Fibroblasts deficient of the HA receptor CD44 displayed impaired migration, stress fibre formation, and production of active TGF-β1, processes that are all dependent on cell adhesion [168]. Consistently, conditional overexpression of HA synthase 2 in α-SMA-positive lung myofibroblasts produced an invasive phenotype that promoted fibrosis progression in bleomycin-treated mouse lungs [169]. The same study showed that conditional deletion of HA synthase 2 under control of the *Col1α2* promoter or inhibition of CD44 inhibited the aggressive myofibroblast phenotype and reduced development of fibrosis. Supported by these findings, HA signalling emerges as a novel target for therapeutic anti-fibrotic interventions.

Syndecans are another class of heparan sulphate proteoglycans that have been shown to affect organ fibrosis [170–172]. Shedding of syndecan-1 (CD138) by matrix metalloproteinases (MMPs) and oxidative stress was shown to contribute to fibrosis development [173,174] and syndecan-1 supports FN fibrillogenesis [175]. The direct effects of syndecans or syndecan fragments on myofibroblast activation have not yet been tested. However, syndecan-2 is known to modulate TGF-β signalling and TGF-β receptor expression presumably by directly binding to TGF-β1 [176]. Furthermore, syndecan-4 knock-out mice exhibit reduced myofibroblast activation after myocardial infarct [177] and in an animal model of lung fibrosis [178].

Small leucine-rich proteoglycans (SLRPs) comprise a group of proteoglycans with a small protein +core and unique tandem leucine-rich repeats. Among the best studied SLRPs are decorin, biglycan, lumican, and fibromodulin [179]. SLRPs fulfil a variety of functions that have a direct impact on ECM and cell homeostasis in fibrocontractive diseases; they regulate cell survival and collagen organization and they bind to growth factors, in particular TGF-β1 [180,181]. SLRPs are often up-regulated in different fibrotic conditions [179], which contradicts the general observation that they act as negative regulators of myofibroblast activation. By contrast, SLRPs are down-regulated in dermal scarring, correlating with fibrotic contractures [182]. This discrepancy may be explained by SLRP performing different functions in different phases of ECM remodelling during repair and fibrosis. For example, decorin potentially regulates myofibroblast activation by virtue of binding to active TGF-β1 [183]. Similarly, biglycan has anti-fibrogenic properties similar to decorin.

Biglycan-deficient cultured cardiac fibroblasts showed enhanced myofibroblast activation and contractile function due to increased TGF-β1 signalling [184]. Much less is known about the role of lumican in fibro-contractive diseases and regulating the myofibroblast phenotype, although it is up-regulated during myofibroblast activation of corneal fibroblasts [185].

Post-translational modification of the myofibroblast ECM

In addition to the composition of the ECM, mechanobiological properties also strongly dictate myofibroblast activation and function. Being contractile cells, myofibroblasts sense and modulate stiffness within the ECM through focal adhesions via integrin binding. Moreover, recent data suggest that mechanical stiffness alone, independent of TGF-β signalling, can induce myofibroblast activation in the setting of fibrosis [186]. Thus, stiffness of the ECM is also a critical modulator of wound healing and fibrosis. Cross-linking of ECM proteins is the major determinant of tissue stiffening. Despite the low turnover rate of collagens in structural tissues such as skin and cartilage, cross-linking of ECM proteins (particularly collagens) is a potentially important area of exploitation for therapeutic purposes in fibrotic disorders. Cross-linking ECM proteins may result in conformational changes that render epitopes ‘hidden’ from protease activity, thereby preventing digestion and remodelling of the ECM. Thus, targeting enzymes and other proteins (discussed below) may provide a means by which fibrotic processes may be effectively halted or perhaps even reversed.

Transglutaminases (TGs) belong to a large family of proteins encoded by structural and functionally related genes [187,188]. The major function of TGs is to catalyse the Ca^{2+}-dependent formation of inter-protein isopeptide bridges between γ-carboxyamide glutamine residues and ε-amino groups in the protein-bound lysine residues [189,190]. TG2 is the most widely and ubiquitously expressed TG family member [191,192]. The ECM substrate spectrum of TG2 is large and comprises FN, vitronectin, collagen types I/II/V/VII/XI, laminin, fibrillin, and LTBP-1, to name only the most prominent [190,193]. Extensive cross-linking of collagen by TG2 produces collagen fibres that are resistant to degradation and that support myofibroblast-mediated fibrosis [194]. In addition to the mechanical consequences of TG cross-linked ECM, the interaction of TG with fibrillins and LTBP-1 modulates the deposition and activation of TGF-β1. Moreover, TGs are directly involved in the proteolytic activation of TGF-β1 from the large latent complex [129], thereby potentially inducing myofibroblast differentiation.

Other important enzymes that promote ECM protein cross-linking in normal and pathological tissue repair belong to the lysyl oxidase (LOX) and lysyl oxidase-like (LOXL) families. LOX is a copper-dependent amine oxidase that forms reactive aldehyde groups from peptidyl lysines in its substrates by oxidative deamidation; these reactive groups spontaneously form covalent cross-links [195,196]. The covalent cross-linking of fibrillar collagen by LOX is of particular importance in fibrotic disease progression [197]. LOX is up-regulated in conditions of tissue repair and fibrosis [198] and induced by TGF-β1 in fibroblast cultures [199–201]. Furthermore, LOX plays a key role in promoting fibroblast-to myofibroblast activation in skin, heart, liver, kidney, and lung fibrosis [195,202–204]. The

conversion of fibroblast-secreted collagen into insoluble fibres by LOX contributes to the accumulation of stiff ECM and thereby contributes to the progression/persistence of fibrosis [198,205,206]. In addition to LOX, LOXL2 has been recently identified to form fibrosis-specific and stable collagen cross-links [207]. LOXL2 oxidatively deaminates the ε-amine group of specific lysine residues of collagen and elastin [208].

Collagen cross-linking also occurs without enzymatic support by glycation; although this process is comparably slow, it is physiologically relevant given the low turnover time of collagen, with a half-life of 15 years in skin and one order of magnitude longer in cartilage [209,210]. A variety of fibrotic and pre-fibrotic conditions such as diabetes are characterized by pathological levels of advanced glycation end-products (AGEs) and tissue stiffening due to glycation [211]. AGEs are pro-fibrotic in that they promote the production of type I and type III collagens [212,213], increase fibroblast proliferation [214], induce TGF-β1-dependent and -independent fibrotic changes [215,216], and induce collagen glycation [217].

Outlook/conclusions

Given the clear role of ECM as a mediator of fibrosis, it seems plausible that these proteins and their modifiers could be possible anti-fibrotic therapeutic targets. However, the ubiquitous nature and clear clinical importance of the ECM dictates that efforts be directed at identifying differences in ECM composition between normal and disease states. As an example, using mass spectrometry, our group has evaluated differences in ECM composition between normal and fibrotic human lung, identifying a number of ECM molecules clearly overexpressed in the diseased organ [218]. Although further study is needed to determine whether these changes reflect pathogenic mechanisms or are merely epiphenomena, we believe that ECM molecules, domains, or cross-links may offer possible novel therapeutic targets for patients with progressive fibrotic disorders.

Among the list of major myofibroblast ECM components, FN seems to be an appropriate target to control myofibroblast development and survival. However, the critical nature of FN to development indicates a need for specific targeting within the molecule. In this regard, the EDA domain of FN is more attractive as a potential therapeutic target for the treatment of fibrotic diseases because it is a specific and crucial component of the myofibroblast ECM that is highly up-regulated in a variety of fibrotic diseases but virtually absent from most normal connective tissues [219–221].

In addition to targeting EDA FN, a second potential target currently under investigation is LOXL2 [222,223]. Initial studies targeting LOX using the inhibitor β-aminopropionitrile (BAPN) reduced collagen cross-linking and scarring but did not proceed to clinical trials due to drug toxicity [224]. However, LOXL2 has also been identified in, and is associated with, fibrotic tissues [208,225]. LOXL2 antibodies are currently being considered for clinical trials in fibrotic disorders [222,223].

Besides interfering with ECM proteins, targeting integrins as specific ECM receptors emerges as another promising therapeutic approach [226]. Many integrins contribute to fibrosis and myofibroblast differentiation through various pathways, including α3β1 [227],

α11β1 [228,229], integrin αvβ3 [230], α4β7 [90], and β1 integrin [186,231]. Of particular interest, αvβ6 integrins, necessary for epithelial activation of TGF-β1 [232], and αvβ5 integrins, involved in mesenchymal cell activation of TGF-β1, have emerged as potential targets in fibrotic disorders. Currently, antibody therapy to αvβ6 integrins is being tested in a phase 2 trial of patients with idiopathic pulmonary fibrosis (Clinicaltrials.gov identifier NCT01371305).

In summary, experimental data suggest that both the myofibroblast and its ECM are critical contributors to pathological fibrogenesis in a variety of organs. Our knowledge in this arena has provided the foundation for upcoming and current clinical trials in patients with fibrotic disorders. Further investigation into the mechanisms by which the ECM promotes fibrosis will likely identify other promising potential targets for therapeutic intervention.

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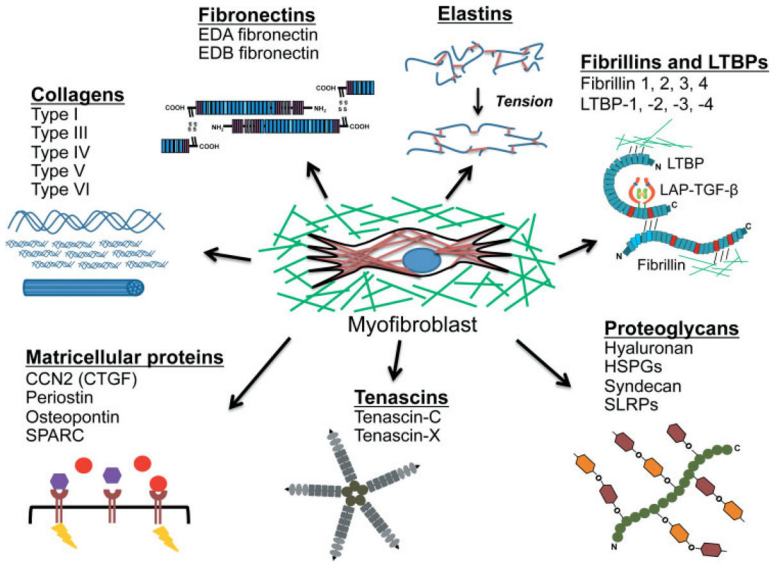

Figure 1.

The myofibroblast matrix. Schematic of some of the ECM molecules relevant to tissue fibrosis. The myofibroblast (centre, with red stress fibres containing α-smooth muscle actin) lies enmeshed in its ECM (green). Components of the ECM are depicted (clockwise, from the 12 o'clock position): elastins, fibrillins and LTBPs, proteoglycans, tenascins, matricellular proteins, collagens, and fibronectins. The myofibroblast encounters, signals, and modulates the expression of these various components as outlined in the text.