Perspective Article

Tissue repair, contraction, and the myofibroblast

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After the first description of the myofibroblast in granulation tissue of an open wound by means of electron microscopy, as an intermediate cell between the fibroblast and the smooth muscle cell, the myofibroblast has been identified both in normal tissues, particularly in locations where there is a necessity of mechanical force development, and in pathological tissues, in relation with hypertrophic scarring, fibromatoses and fibrocontractive diseases as well as in the stroma reaction to epithelial tumors. It is now accepted that fibroblast/myofibroblast transition begins with the appearance of the protomyofibroblast, whose stress fibers contain only β- and γ-cytoplasmic actins and evolves, but not necessarily always, into the appearance of the differentiated myofibroblast, the most common variant of this cell, with stress fibers containing α-smooth muscle actin. Myofibroblast differentiation is a complex process, regulated by at least a cytokine (the transforming growth factor-β1), an extracellular matrix component (the ED-A splice variant of cellular fibronectin), as well as the presence of mechanical tension. The myofibroblast is a key cell for the connective tissue remodeling that takes place during wound healing and fibrosis development. On this basis, the myofibroblast may represent a new important target for improving the evolution of such diseases as hypertrophic scars, and liver, kidney or pulmonary fibrosis. **(WOUND REP REG 2005;13:7–12)**

FACTORS INVOLVED IN MYOFIBROBLASTIC DIFFERENTIATION

The myofibroblast was initially identified by means of electron microscopy in granulation tissue of healing wounds as a modulated fibroblast, exhibiting features of smooth muscle (SM) cells, such as bundles of microfilaments, with dense bodies scattered in between, and gap junctions.[1] The presence of myofibroblasts has successively been described in practically all fibrotic situations characterized by tissue retraction and remodeling (for review, see[2]). The work of many laboratories has contributed to define this cell morphologically, by showing that its contractile structures are represented by stress fibers, and biochemically, by showing that stress fibers express contractile proteins typical of SM cells, particularly of vascular SM cells, such as α-SM actin (α-SMA).[3] Presently it is accepted that the myofibroblastic modulation of fibroblastic cells begins with the appearance of the protomyofibroblast, whose stress fibers contain only β- and γ-cytoplasmic actins and evolves, but not necessarily always, into the appearance of the differentiated myofibroblast, the most common variant of this cell, with stress fibers containing α-SMA (for review, see[4]; Figure 1). Myofibroblasts can, according to the experimental or clinical situation, express other SM cell contractile proteins, such as SM-myosin heavy chains or desmin; however, the presence of α-SMA represents the most reliable marker of the myofibroblastic phenotype.[4]

ECM	Extracellular matrix
MMP	Matrix metalloproteinase
SM	Smooth muscle
α-SMA	α-SM actin
TGF-β	Transforming growth factor-β
TIMP	Tissue inhibitor of metalloproteinases

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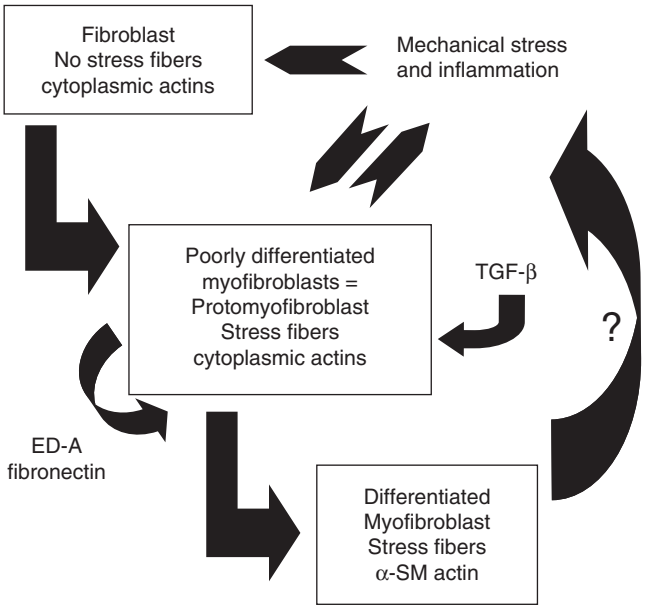

FIGURE 1. Schematic illustration showing the evolution of the (myo)fibroblast phenotype. The myofibroblastic modulation of fibroblastic cells begins with the appearance of the protomyofibroblast, whose stress fibers contain only β- and γ-cytoplasmic actins and evolves, but not necessarily always, into the appearance of the differentiated myofibroblast, the most common variant of this cell, with stress fibers containing α-SM actin. Myofibroblast differentiation is regulated by both cell products (e.g., TGF-β) and ECM components (e.g., fibronectin ED-A). It is emphasized that (myo)fibroblasts themselves can play an immunoregulatory role.[44] (Modified from[4])

Although the modulation toward the protomyofibroblast is at present not well explored, the switch from the protomyofibroblast to the differentiated myofibroblast has been related to the production by inflammatory cells, and possibly by fibroblastic cells, of transforming growth factor-β1 (TGF-β1), the most accepted stimulator of myofibroblastic differentiation.[5] The action of TGF-β1 depends on the local presence of the cellular fibronectin splice variant ED-A.[6] Thus, myofibroblast differentiation is regulated by both a cell product and an extracellular matrix (ECM) component (Figure 1).

Recently, the mechanisms by which endothelin-1[7] and thrombin[8] are able to promote myofibroblast induction have been explored. Moreover, it is becoming more accepted that mechanical factors play an important role in both transitions.[9] An increasing number of patients are being treated with growth hormone for the enhancement of body growth but also as an antiageing strategy. Interestingly, it has been recently shown that growth hormone inhibits TGF-β–induced myofibroblast differentiation, resulting in a reduction in fibroblast contractile activity; in transgenic mice overexpressing growth hormone, excisional wound closure is strongly delayed.[10]

The question concerning the reversibility of the myofibroblastic differentiation is important, particularly for the treatment of diseases involving myofibroblasts. We can assume that fibroblasts remaining in granulation tissue after reepithelialization have reverted to a more quiescent, noncontractile phenotype lacking the microfilament bundles that were present during the contractile phase of healing. However, until now, this positive and negative modulation of the myofibroblast phenotype has not been clearly shown in vivo, even if in vitro it seems possible to revert the myofibroblast phenotype. It is also conceivable that the residual fibroblasts represent a subpopulation of cells that failed to acquire a myofibroblast phenotype during healing and thus survive, while the myofibroblastic cells that appeared during healing represent terminally differentiated cells undergoing apoptosis during the resolution phase.

ROLE OF THE MYOFIBROBLAST IN WOUND CONTRACTION

Recently, it has been shown that α-SMA participates importantly in force production by the myofibroblast both in vitro, using models involving fibroblasts cultured on flexible substrates or within floating and attached collagen gels,[11] and in vivo, using experimental wound healing in the rat.[12] Indeed cells expressing this protein, i.e., differentiated myofibroblasts, produce a stronger retractile activity compared to protomyofibroblasts in the absence of any other change in contractile protein expression. Another important point is that the isometric tension produced by the myofibroblast is regulated differently compared to the reversible contraction produced by classical SM cells. While SM cell contraction is Ca^{++} dependent and is reversible, tension production by the myofibroblast is not reversible and is regulated by a Rho/Rho kinase-mediated inhibition of myosin phosphatase.[13,14]

MYOFIBROBLAST CONTRACTION AND HYPERTROPHIC SCAR FORMATION

One of the important problems that have not been solved in the understanding of myofibroblast biology is the mechanism of its appearance and persistence in pathological situations involving hypertrophic scarring and development of fibrosis. Particularly, in hypertrophic scars that develop after burn, myofibroblastic cells expressing α-SMA are numerous and are involved in contracture formation (Figure 2). A possibility is the inhibition of the apoptosis of these cells that characterizes the terminal phases of wound healing.[15] This is difficult to prove in clinical situations and, unfortunately, at present there are no reliable models of hypertrophic scarring in experimental animals. Moreover, even if the observation that myofibroblasts undergo

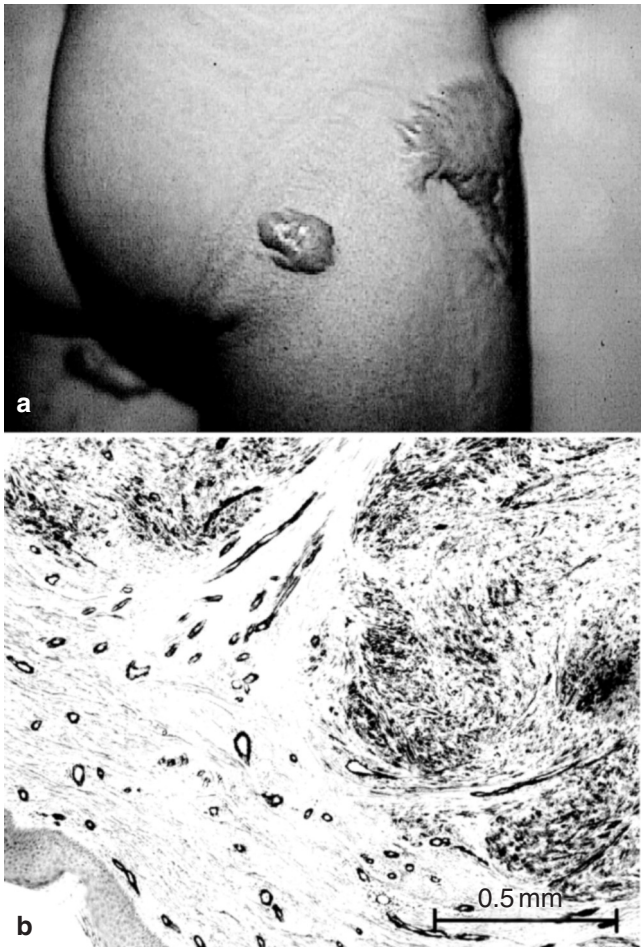

FIGURE 2. Photographic and histologic appearance of hypertrophic scars. (a) Typical hypertrophic scars observed after burn, and showing contractures. (b) Hypertrophic scar usually presents nodules containing numerous α-SMA-expressing myofibroblasts participating in contracture activity (immunostained with α-SMA antibody).

apoptosis during wound healing when epithelialization is completed is well established, little is known about the mechanisms regulating this phenomenon. The signal for this cell death may be related to reduction in the concentration of local trophic factors, as reepithelialization and depletion of inflammatory cells occur in later phases of wound healing. The remodeling of the ECM by matrix metalloproteinases (MMPs) may also play a role by interfering with myofibroblast adhesion to the ECM as has been suggested by studies on regression of granulation tissue under a vascularized skin flap.[16]

Early in wound repair, the balance between MMPs such as collagenases and gelatinases and their endogenous inhibitors, tissue inhibitors of metalloproteinases (TIMPs), favors ECM production. Later in wound healing as remodeling occurs, it is possible that this balance changes and favors matrix degradation. As mentioned above, this could potentially result in increased apoptosis. Changes in the physical stress caused by stretch of granulation tissue may also contribute to the loss of cells via an apoptotic mechanism as has been suggested by in vitro studies of fibroblasts in collagen lattices.[17] Furthermore, a cross talk between epidermis and dermis exists through the basement membrane.[18,19] A persistence of activated keratinocytes has been observed in hypertrophic scar epidermis implicating abnormal epidermal–mesenchymal interactions, and suggesting that cellular mechanisms in the pathogenesis of hypertrophic scarring are more complex than isolated dermal phenomena.[20] Recently, however, differential responses to apoptotic inducers were observed between normal skin wound and hypertrophic scar myofibroblasts, confirming the hypothesis of defects in apoptosis and growth during pathological scar formation impeding myofibroblast disappearance at the end of healing.[21]

MYOFIBROBLAST CONTRACTION AND FIBROSIS

The role of the fibroblast in determining organ shape during embryonic development has been suspected for many years and is presently more and more accepted.[22] The most plausible mechanism of this morphogenetic action is ECM shape remodeling, which in turn influences epithelial architecture. The work on the myofibroblast extends this possibility to adult tissues and gives new indications on the possible mechanisms for this action. The correct repair of connective tissue in a given organ requires the proper reconstitution of its support function and an appropriate tensile strength must be recreated. α-SMA-expressing myofibroblasts not only promote contraction but also synthesize elevated levels of both ECM components and matrix degrading proteases. The persistence of myofibroblasts within a fibrotic lesion leads to excessive scarring with the functional impairment of the affected organ. Thus, the interactions between the myofibroblast and its surrounding ECM play an important role in the resultant mechanical properties of the connective tissue.[9] Interestingly, it has been shown that liver cirrhosis characterized by excessive secretion of matrix proteins by liver myofibroblasts, previously considered irreversible, can be remodeled with decreased expression of type I collagen and TIMP mRNA, activation of MMPs, and myofibroblast apoptosis; residual septa were characterized by important tissue transglutaminase-mediated matrix cross-linking.[23]

It is well known that many epithelial tumors are characterized by the local accumulation of connective tissue cells and extracellular material; this phenomenon has been called the stroma reaction. One of the cellular components of the stroma reaction is the myofibroblast. Myofibroblasts interact with epithelial cells and other connective tissue cells and may thus control such

phenomena as tumor invasion and angiogenesis[24,25] (for review, see[26]). On this basis, the myofibroblast may represent a new important target of antitumor therapy.

In the liver, as in many organs, different subpopulations of fibroblastic cells can acquire a myofibroblastic phenotype (e.g., hepatic stellate cells and portal fibroblasts). It appears that in these different populations, the mechanisms leading to α-SMA expression and persistence in pathological situations are different. Schematically, among the cells able to acquire α-SMA, we can distinguish fibroblastic cells and pericyte-like cells (e.g., hepatic stellate cells or glomerular mesangial cells). The latter can modulate their α-SMA expression in response to blood pressure modifications while the former are engaged in a more irreversible phenotypic change. However, both populations can be involved in fibrotic processes. It is important to underline that in different organs, fibroblasts represent a heterogeneous population of cells defined according to their location within the organ.[27–29] Among these populations, phenotypic differences are obvious, concerning, for example, ECM synthesis and remodeling, production of growth factors and cytokines, and involvement in tissue repair processes. This distinction between fibroblast subtypes has important consequence in normal tissue homeostasis or excessive scarring.

ORIGIN OF THE MYOFIBROBLAST

Myofibroblasts of wound tissue have been assumed to originate from local recruitment of fibroblasts in the surrounding dermis and subcutaneous tissue.[30] This is supported by the presence of many fibroblasts showing proliferation marker-positive nuclei at the periphery of the wound. Pericytes or vascular SM cells around vessels represent another possible source of myofibroblasts. During renal fibrogenesis, it has been shown that fibroblasts arise in large numbers by local epithelial-mesenchymal transition (for review, see[31]). However, further work is necessary to clearly define the process of epithelial-mesenchymal transition (or transdifferentiation) and to evaluate its role during pathological tissue repair.

Circulating precursor cells, called fibrocytes, have been suggested to migrate into the wound and to contribute to the formation of the myofibroblastic population of granulation tissue.[32] These cells can be induced by TGF-β1 to express α-SMA, and they readily contract collagen gels in vitro.[33] Clinically, there is evidence that patients with hypertrophic scars and other fibrosing disorders have fibrocytes in their lesions (for review, see[34]). It has been suggested that circulating fibrocytes represent an important source of fibroblasts during healing of extensive burn wounds where it may be difficult for fibroblasts to migrate from the edges of the injury.[35] The role of fibrocytes has also been underlined in asthma.[36] Recently, by analyzing the tissue of humans and mice that received either sex-mismatched organ transplants or bone marrow transplants, bone marrow-derived myofibroblasts participating in fibrogenic reactions have been identified in several organs.[37–39] Finally, it has been shown that progenitor cells located in the dermal sheath that surrounds the outside of the hair follicle not only maintain and regenerate the dermal papilla but also can perform important functions in the repair of skin dermis after injury.[40] Furthermore, interesting data show the potential usefulness of these follicle dermal cells in the construction of human skin equivalents and skin substitutes.[41] It should be stressed, however, that irrespective of the origin of the lesion, the major source of fibroblasts in granulation tissue is recruitment by chemotaxis and subsequent migration from the surrounding connective tissue.

CONCLUSION

During the last few years, important advances have been made in the understanding of several aspects of myofibroblast biology. It remains to apply the new biological knowledge to the modulation of myofibroblast activities that regulate the evolution of fibrotic disease. Several avenues are practicable, such as influencing myofibroblast apoptosis and/or replication or collagen and/or proteolytic enzyme production by myofibroblasts.

The N-terminal sequence AcEEED of α-SMA is crucial for α-SMA polymerization.[42] AcEEED administered as a fusion peptide with a cell penetrating sequence selectively inhibits α-SMA incorporation into stress fibers, reducing the tension exerted by cultured myofibroblasts on their substratum coupled with a significant decrease in collagen type I synthesis by the same cells.[43] Moreover, intracellular delivery of AcEEED produces a significant reduction of the contractile capacity of granulation tissue strips after endothelin-1 stimulation and a significant delay of wound contraction in rat wounds splinted for 10 days and treated for the last 3 days with the fusion peptide.[43] We hope that further work in this direction as well as in other aspects of myofibroblast biology will eventually result in efficient pharmacological tools improving the evolution of such diseases as hypertrophic scars, and liver, kidney, or pulmonary fibrosis.

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