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Review Article

Myofibroblasts in diseases

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ABSTRACT:
The discovery of the myofibroblast has allowed definition of the cell responsible for wound contraction and for the development of fibrotic changes. 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. Repeated cycles of injury and repair lead to organ or tissue fibrosis through secretion of ECM by the myofibroblasts. Transforming growth factor-beta and the PDGF family of growth factors are the key factors in the fibrotic response. Because of their ubiquitous presence in all tissues, myofibroblasts play important roles in various organ diseases and perhaps in multisystem diseases as well.
Key words: Myofibroblasts, Diseases

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INTRODUCTION

During normal tissue repair, such as skin wound healing, controlled and transient activation of myofibroblasts contributes to restoration of tissue integrity by forming a mechanically sound scar. For example, scars stabilize the heart muscle after myocardial infarction and tendon, bone, and cartilage after fracture or rupture. However, when myofibroblast activities become excessive and persist, beneficial tissue repair turns into the detrimental tissue deformities characteristic of organ fibrosis. In this review, we will discuss in more detail fibrosis of the skin, lungs, liver, and kidney. Another fibrotic condition is the desmoplastic or stromal reaction to epithelial tumors, during which myofibroblasts contribute to the mediator and mechanical environment that promotes tumor progression.

Specific Aspects of Myofibroblast Contraction

High contractile activity of myofibroblasts is necessary for generating tissue contractures. In addition to the expression of α-smooth muscle actin (α-SMA; gene ACTA) in stress fibers, which promotes stronger force generation compared with other actin isoforms in fibroblastic cells, myofibroblasts appear to use specific modes of contraction.3,7 In contrast to the reversible and comparably short-lived contraction of striated and smooth muscles, myofibroblast contractile activity, together with ECM synthesis and degradation, leads to connective tissue remodeling, followed by irreversible and long contractures in a process that can span weeks, months, or even years. It is still unknown how myofibroblasts stabilize contractions that occur at the cellular or subcellular level to counteract the stress present in a tissue undergoing remodeling. Recent in vitro studies8 indicate that myofibroblasts use a lockstep or ratchet mechanism of cyclic and incremental contractile events. This mechanism consists of strong (micronewtons) and far-ranging (tens of micrometers) contractions mediated by RhoA/Rho-associated kinase and weak (approximately 100 pN) and short-ranging (approximately 0.4 μm) cyclic contractions promoted by changes in intracellular calcium concentrations.8 The model proposes that strong isometric contraction generates slack in the myofibroblast-associated fibrous and stressed collagen. Such tension-released fibrils are then straightened by the weak, but repeated, subcellular contractile events. By local ECM remodeling and/or deposition of new ECM, the shortened and repeatedly stressed collagen fibrils stabilize the status quo of the ECM, and a new

myofibroblast contraction cycle can begin. It is intriguing that the level of stress (ie, the resistance of collagen fibers to pulling) may determine which mechanism of contraction will be engaged.

SIGNIFICANCE OF MYOFIBROBLAST DIFFERENTIATION

Myofibroblast differentiation represents a key event during wound healing, tissue repair, as well as chronic fibrosis. The high contractile force generated by myofibroblasts is beneficial for physiological tissue remodeling but detrimental for tissue function when it becomes excessive such as in hypertrophic scars, in virtually all fibrotic diseases, and during stromal reaction to tumors. The myofibroblast are shown to be the major extracellular matrix producing cells in fibrotic diseases in a variety of organs. However, despite evidence suggesting that suppression of myofibroblast differentiation correlates with reduced fibrosis, direct proof is lacking that this is due specifically to the suppression of de-novo genesis of the myofibroblast. More direct evidence was obtained recently in a study using mesenchymal cell/fibroblast-specific conditional CCAAT/Enhancer Binding Protein β (C/EBPβ) knock out mice. These mice had reduced myofibroblasts and pulmonary fibrosis but an intact inflammatory/immune cell response when endotracheally injected with bleomycin. Thus, despite the broad spectrum of C/EBPβ target genes in multiple cell types, its selective depletion in fibroblasts results in diminished myofibroblast differentiation and fibrosis.

The focus of recent studies is on critical mechanisms underlying genesis of myofibroblasts. These studies elucidate the importance of the major signaling pathways, including TGFβ, Wnt, Notch, and hedgehog pathways along with their downstream transcription factor targets that mediate their effects on gene expression. Additionally, mounting evidence for epigenetic regulatory mechanisms has been identified in the control of myofibroblast differentiation. Future studies should reveal more of the complexities underlying these mechanisms and how they interact to ultimately regulate myofibroblast differentiation and fate.

Associated pathologies

Many diseases associated with diminished or excess deposition of ECM are likely to be related to dysregulation of the injury repair response and fibroblast function. In this context ‘injury’ is broad ranging including environmental, infectious, cancerous, traumatic/mechanical, autoimmune and drug-induced insults. Thus, diseases in which fibroblasts, in their various phenotypic guises, play a central role may affect almost all tissues and organs of the body. Their importance is further highlighted by the suggestion that almost half of all deaths are associated with fibrosing conditions. Diseases associated with either increased or decreased ECM deposition, or contraction of tissues result in distorted tissue architecture, impaired function and in many cases, particularly where the vital organs are involved, significant morbidity and mortality. Dysregulation of several phases of the injury repair response, including chronic or repetitive injury, an inappropriate inflammatory response, an altered balance of ECM metabolism and deposition, altered phenotypic profiles or persistence of myofibroblasts contribute to aberrant tissue repair.

At present there are no treatments which specifically target fibroblast-associated pathologies. Current therapeutic strategies primarily revolve around the use of antiinflammatory corticosteroids, immunosuppressants and treatment of tissue or disease specific symptoms. However, at best these have limited therapeutic effects. Over the last 30 years a number of approaches to modulate extracellular matrix synthesis or degradation, including use of prolyl-4-hydroxylase inhibitors to limit collagen synthesis and TIMP inhibitors to promote ECM degradation have been developed, although none have yet progressed the clinic. The rapid expansion of our knowledge over the last 15–20 years of mediators involved in the regulation of the normal injury repair process and in the pathogenesis of diseases associated with aberrant repair has identified novel therapeutic targets and led to the development of a number of specific inhibitors for mediators or their receptors. These include small molecule antagonists and biological inhibitors targeting TGF, endothelin-1, interferon- , EGF, and IL-13 which are currently in or about to enter clinical trials. For example, inhibitors of TGF- activity including neutralizing antibodies and antisense vaccines are currently undergoing clinical trials and small molecule receptor antagonists are in pre-clinical development. These are likely to impact on a number of processes, including inhibition of the conversion of fibrocytes to myofibroblasts, EMT, and modulation of ECM metabolism and deposition.

In addition, the recent development of siRNA technologies may allow for more rapid drug development with the potential to dramatically reduce the time from target identification to clinical trials. For example, siRNAs developed for use in other disease settings by Sirna Therapeutics (Sirna-027, which targets vascular endothelial growth factor receptor 1, VEGFR-1) and Alnylam (ALNRSV01, which targets respiratory syncytial virus) took less than 2 years from development to Phase I clinical trials.

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