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Understanding Fibroblast Activation in Physiological and Pathological Processes.

Salim Yusuf*

Professor of Medicine, McMaster University, Canada

***Correspondence to:** Salim Yusuf, Professor of Medicine, McMaster University, Canada. Email: yusufs@mcmaster.ca

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Introduction

Fibroblasts are critical cellular components of connective tissue, primarily recognized for their role in the maintenance of extracellular matrix (ECM) homeostasis. These spindle-shaped cells are the primary source of collagen and other ECM proteins, playing a key role in tissue repair and structural integrity. However, under certain physiological and pathological conditions, fibroblasts undergo a process known as fibroblast activation. This transformation leads to a more proliferative, contractile, and secretory phenotype often referred to as myofibroblasts. While fibroblast activation is an essential part of wound healing and tissue repair, its chronic or dysregulated persistence is associated with a variety of pathological conditions, most notably organ fibrosis, cancer, and inflammatory diseases. Diagnostic markers of fibroblast activation are increasingly being explored. Elevated levels of serum biomarkers such as pro-collagen peptides, fibronectin, and periostin have been associated with disease severity in fibrosis. Imaging modalities using labeled probes targeting fibroblast activation protein (FAP) are also being developed to visualize fibrotic tissue in vivo. Such tools could help in early diagnosis, monitoring of disease progression, and evaluation of therapeutic response.

Fibroblast activation is generally triggered by a combination of mechanical stress, cytokines, growth factors, and damage-associated molecular patterns (DAMPs). One of the most well-characterized pathways involves transforming growth factor-beta (TGF-β), a potent profibrotic cytokine. Upon activation, fibroblasts increase the production of alpha-smooth muscle actin (α-SMA), a hallmark of myofibroblast differentiation, along with an increase in ECM proteins such as fibronectin and various types of collagen. The activated fibroblast also expresses various proteolytic enzymes, chemokines, and growth factors, further amplifying the local tissue response.

In the context of normal wound healing, fibroblast activation is a tightly regulated and transient process. Once the tissue is repaired, activated fibroblasts are either eliminated via apoptosis or revert to a quiescent phenotype. However, when the activation signals are persistent or unresolved, as in chronic inflammation or repetitive injury, fibroblasts continue to deposit ECM components excessively, leading to fibrosis. This pathological accumulation of ECM disrupts the normal architecture and function of organs such as the liver, lungs, kidneys, and heart.In pulmonary fibrosis, for example, activated fibroblasts and myofibroblasts are central players in the fibrotic remodeling of lung tissue. Idiopathic pulmonary fibrosis (IPF) is characterized by fibroblast foci, areas densely populated with activated fibroblasts and myofibroblasts, which secrete collagen and contractile proteins. These changes result in stiffening of lung tissue and progressive loss of respiratory function. Similarly, in liver fibrosis, hepatic stellate cells (a specialized form of pericytes with fibroblast-like properties) become activated in response to chronic liver injury and transform into collagen-producing myofibroblasts, contributing to cirrhosis.

Cardiac fibrosis is another pathological condition where fibroblast activation plays a detrimental role. After myocardial infarction or in conditions of chronic hypertension, cardiac fibroblasts become activated and contribute to ECM deposition, disrupting the normal conduction and contractile function of the heart. This results in reduced cardiac compliance, arrhythmogenesis, and ultimately heart failure.Beyond fibrosis, fibroblast activation is increasingly recognized as a critical factor in cancer progression. In the tumor microenvironment, cancer-associated fibroblasts

(CAFs) support tumor growth, angiogenesis,

invasion, and immune evasion. CAFs share many features with activated fibroblasts, including the expression of α-SMA and secretion of ECM proteins and cytokines. They can remodel the tumor stroma to facilitate tumor cell migration and produce immunosuppressive molecules that hinder anti-tumor immunity. Furthermore, CAFs are implicated in resistance to chemotherapy and immunotherapy by forming physical and biochemical barriers to drug delivery and immune cell infiltration.

Several molecular pathways are involved in fibroblast activation, including TGF-β/Smad, Wnt/β-catenin, Notch, and PI3K/Akt signaling. These pathways are often interconnected, forming a complex regulatory network that governs fibroblast behavior. The TGF-β pathway remains a primary focus for antifibrotic therapy development. Other potential targets include lysyl oxidase-like proteins involved in ECM crosslinking, integrins mediating cell-ECM interactions, and epigenetic modifiers that influence fibroblast gene expression profiles.The reversibility of fibroblast activation is an area of active research. Understanding the factors that allow fibroblasts to revert to a quiescent state or undergo apoptosis after their function is completed could provide new therapeutic strategies for fibrotic diseases. For instance, studies have shown that certain transcription factors and microRNAs may promote fibroblast deactivation or senescence. Targeting these molecules could aid in reprogramming the fibrotic stroma into a more normalized state.

Conclusion

Fibroblast activation is a fundamental biological process with far-reaching implications in health and disease. It represents a key adaptive response to injury, orchestrating wound healing and tissue remodeling. However, when dysregulated, it contributes to the pathogenesis of numerous chronic diseases, including organ fibrosis, cancer, and autoimmune disorders. A nuanced understanding of fibroblast activation and its regulatory mechanisms is critical for designing effective therapeutic strategies

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