Editorial

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TGF-β Signaling in Fibroblasts: Central Regulators of Tissue Remodeling and Fibrosis

Lucas Schneider*

Department of Molecular Medicine, University of Munich, Germany

***Author for Correspondence:**
lucas.schneider@lmu.de

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Introduction

Transforming growth factor-beta (TGF-β) is a pivotal cytokine that regulates fibroblast function in development, tissue repair, and disease. Fibroblasts respond to TGF-β signaling by modulating extracellular matrix production, proliferation, and differentiation into myofibroblasts. Dysregulated TGF-β signaling in fibroblasts is a major driver of pathological fibrosis in organs such as the lung, liver, kidney, and heart. Understanding this signaling pathway in fibroblasts is crucial for developing therapies targeting fibrotic and remodeling diseases.

Mechanisms and Fibroblast Activation

TGF-β binds to its receptor complex on fibroblasts, triggering canonical SMAD-dependent and non-canonical signaling cascades. Activation of SMAD2/3 promotes transcription of genes encoding collagen, fibronectin, and α-smooth muscle actin, leading to myofibroblast differentiation and matrix deposition. Non-canonical pathways, including MAPK and PI3K/AKT signaling, further modulate fibroblast proliferation, survival, and migration.

Fibroblast subsets exhibit differential sensitivity to TGF-β, contributing to functional heterogeneity within tissues. Some fibroblasts maintain regenerative functions, while others drive excessive matrix deposition and fibrosis. Single-cell transcriptomics has been instrumental in identifying these subsets and linking TGF-β responsiveness to pathogenic outcomes.

Clinical Implications

Aberrant TGF-β signaling in fibroblasts is a hallmark of fibrotic diseases such as idiopathic pulmonary fibrosis, systemic sclerosis, and liver cirrhosis. Therapeutic strategies targeting TGF-β or its downstream effectors are being explored, including neutralizing antibodies, receptor kinase inhibitors, and SMAD modulators. Precision approaches aim to inhibit pathogenic fibroblast activation while preserving essential tissue repair functions.

Moreover, understanding the interplay between TGF-β signaling and fibroblast heterogeneity offers insights into tumor-associated fibroblasts, where TGF-β drives extracellular matrix remodeling and immune suppression, influencing cancer progression.

Conclusion

TGF-β signaling in fibroblasts is a central regulator of tissue homeostasis and pathological remodeling. The balance between regenerative and fibrotic fibroblast responses determines disease outcomes across multiple organs. Advances in single-cell profiling and targeted therapeutics offer new opportunities to modulate TGF-β-driven fibroblast activity, paving the way for effective treatments for fibrosis, cancer, and tissue repair disorders.