

# Single-cell RNA Sequencing Reveals Monocyte-derived Pro-fibrotic Interstitial Macrophages

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## Introduction

The intricate mechanisms underlying fibrosis, particularly in tissues such as the lung, liver and kidney, continue to challenge both basic researchers and clinicians. Fibrosis, the pathological accumulation of extracellular Matrix (ECM) proteins such as collagen, contributes to the dysfunction of tissues and organs, culminating in diseases such as Idiopathic Pulmonary Fibrosis (IPF), liver cirrhosis and chronic kidney disease. Understanding the cellular and molecular events that drive fibrosis is essential for identifying new therapeutic targets. Macrophages, as key players in tissue inflammation and immune responses, have long been implicated in the pathogenesis of fibrosis. Traditionally, macrophages are thought to exert their pro-fibrotic effects through the secretion of cytokines and growth factors, which promote the activation of fibroblasts and the subsequent deposition of ECM. However, the precise identity of the macrophage subpopulations involved in fibrosis and their origins, remain incompletely understood [1].

Recent advances in single-cell RNA sequencing (scRNA-seq) technologies have revolutionized our ability to profile the transcriptomes of individual cells within heterogeneous tissues, providing unprecedented insights into cellular diversity and plasticity. One of the remarkable discoveries facilitated by scRNA-seq in the context of fibrosis has been the identification of specific macrophage subpopulations with pro-fibrotic characteristics. These macrophages have been shown to arise from circulating monocytes and migrate to sites of injury, where they adopt a distinct transcriptomic profile that supports fibrosis. This reviews the emerging role of monocyte-derived macrophages in fibrosis, focusing on the application of single-cell RNA sequencing to dissect their differentiation, functional characteristics and contribution to tissue remodeling. The implications of these findings for therapeutic strategies aimed at modulating macrophage responses in fibrosis will also be discussed [2].

## Description

Fibrosis refers to the pathological accumulation of ECM components in response to chronic injury or inflammation. This process is characterized by the activation and proliferation of fibroblasts, myofibroblasts and other mesenchymal cells that produce and deposit ECM proteins, leading to tissue scarring. Fibrosis occurs in many organs, including the lungs, liver, heart and kidneys and is often the result of chronic inflammation driven by immune cells, particularly macrophages. Macrophages are key regulators of tissue homeostasis, immune defense and repair following injury. They derive from hematopoietic stem cells in the bone marrow and can be classified into two broad categories based on their activation states, M1 (classically activated) macrophages, which are pro-inflammatory and respond to pathogens and M2 (alternatively activated) macrophages, which are generally associated with

tissue repair and immune regulation [3].

The concept of macrophage polarization has evolved over the past decade, with increasing evidence pointing to a much more complex spectrum of macrophage phenotypes in response to different microenvironmental cues. In the context of fibrosis, macrophages have been shown to adopt specific pro-fibrotic phenotypes that support the activation of fibroblasts and ECM deposition. These macrophages, often referred to as "fibrotic macrophages," play a central role in promoting tissue remodeling and fibrosis in a variety of organs. Single-cell RNA sequencing has emerged as a powerful tool for dissecting cellular heterogeneity within complex tissues, enabling researchers to identify rare and previously unrecognized cell types or states. This technology allows for the examination of gene expression at the single-cell level, providing insights into the molecular mechanisms driving cellular behavior. In the context of fibrosis, scRNA-seq has been instrumental in uncovering the diversity of macrophage subpopulations that contribute to tissue scarring. By applying scRNA-seq to fibrotic tissues from various organs, researchers have identified distinct macrophage subsets with pro-fibrotic gene expression signatures. These subsets include macrophages that are derived from circulating monocytes, as well as those that arise from resident tissue macrophages [4].

One of the most striking discoveries from recent scRNA-seq studies is the identification of a specific subset of macrophages that are derived from monocytes and are strongly associated with fibrosis. These monocyte-derived macrophages (MDMs) are recruited to the site of injury or inflammation, where they differentiate into pro-fibrotic macrophages that promote ECM deposition and tissue remodeling.

Monocytes are circulating precursors of macrophages that can rapidly migrate to sites of infection, injury, or inflammation. Upon arrival at these sites, monocytes differentiate into tissue-resident macrophages, which can exhibit a broad range of functional states depending on the local microenvironment. In the context of fibrosis, monocytes are recruited to injured tissues in response to inflammatory signals, where they undergo a series of transcriptional changes that prime them for the pro-fibrotic response. The scRNA-seq studies have revealed that monocyte-derived macrophages exhibit distinct gene expression profiles compared to resident tissue macrophages. These pro-fibrotic MDMs express high levels of genes associated with ECM remodeling, such as collagens, fibronectin and metalloproteinases, as well as growth factors like TGF- $\beta$ , IL-1 $\beta$  and PDGF, which further stimulate fibroblast activation and collagen deposition [5].

## Conclusion

Single-cell RNA sequencing has provided a powerful tool to investigate the cellular and molecular mechanisms of fibrosis, leading to the identification of monocyte-derived macrophages as key drivers of fibrotic tissue remodeling. These macrophages, which differentiate from circulating monocytes and acquire a pro-fibrotic gene expression signature, play a central role in the progression of fibrosis in multiple organs, including the lung, liver and kidney. The insights gained from scRNA-seq studies have profound implications for therapeutic strategies aimed at modulating macrophage behavior in fibrosis. Targeting the recruitment, differentiation, or function of pro-fibrotic monocyte-derived macrophages may represent a promising approach to attenuate the progression of fibrotic diseases and improve patient outcomes. As our understanding of macrophage heterogeneity and plasticity continues to evolve, it is likely that new, more effective therapies will emerge, offering hope for patients suffering from the debilitating consequences of fibrosis.

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## Conflict of Interest

None.

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