The Pathogenesis of Renal Fibrosis: A Current Debate on Fibroblast Origins

Hui Yao Lan, MD, PhD

Department of Medicine and Therapeutics, and Li Ka Shing Institute of Health Sciences,
The Chinese University of Hong Kong, Hong Kong

It is well documented that myofibroblasts, an activated form of fibroblasts, are a key collagen-producing cell type responsible for progressive renal fibrosis. However, the origin of this fibrotic phenotype during renal fibrosis remains controversial. To better understand the pathogenesis of renal fibrosis, this review outlined the potential pathways and mechanisms regulating the myofibroblast origin during progressive renal fibrosis.

1. Epithelial-mesenchymal transition (EMT) as a major mechanism leading to renal fibrosis. In the past decades, EMT has been considered as the critical pathway of renal myofibroblast origin in animal models of kidney diseases, but not in renal biopsy tissues from patients with CKD. TGF-β1 is a key growth factor mediating this process. Furthermore, we recently also found that other fibrogenic factors such as angiotensin II and advanced glycation end products (AGE) can mediate EMT via both TGF-β-dependent and independent mechanisms.

2. Pericyte as a major pathway of renal fibroblast origin. Recently, the EMT pathway has been largely debated due to the lack of evidence in human CKD. In contrast, pericyte may be a major pathway of renal fibroblast origin. This is demonstrated in a number of transgenic mouse models of obstructive nephropathy in which myofibroblasts are highly expressed pericyte markers such as PDGF-Rβ but lack of tubular epithelial phenotype genetically. However, if this represents a sole phenotype for the origin of myofibroblasts remains to be determined.

3. The endothelial-mesenchymal transition (EndoMT). EndoMT may also contribute to the origin of myofibroblasts and participate in the process of renal fibrosis in a mouse model of diabetic kidney disease. However, the role of EndoMT in renal fibrosis remains unclear although blockade of TGF-β/Smad3 signaling inhibits this process in vitro.

4. Bone marrow-derived cells and circulating fibrocytes in renal fibrosis. Increasing evidence shows that bone marrow-derived cells may contribute to the generation of myofibroblasts during renal fibrosis. It is possible that the circulating fibrocytes may be a source of blood-derived fibroblast origin. However, the mechanisms regulating this pathway remain largely unclear.

In summary, although many pathways may contribute to the origin of myofibroblasts during renal fibrosis, the origin of renal fibroblasts remain yet elusive because no strong evidence of these phenotypes has been proven to be critical in human renal biopsies. It is highly possible that multiple mechanisms/pathways may contribute to myofibroblast accumulation during renal fibrosis under a variety of disease conditions. Thus, further studies to clarify the pathways leading to renal fibroblast accumulation and fibrosis relevant to human chronic kidney disease remain needed.