

Recent Advances in Magnetic Resonance Imaging Assessment of Renal Fibrosis



Jia Li, Changlong An, Lei Kang, William E. Mitch, and Yanlin Wang

CKD is a global public health problem. Renal fibrosis is a final common pathway leading to progressive loss of function in CKD. The degree of renal fibrosis predicts the prognosis of CKD. Recent studies have shown that bone marrow-derived fibroblasts contribute significantly to the development of renal fibrosis, which may yield novel therapeutic strategy for fibrotic kidney disease. Therefore, it is imperative to accurately assess the degree of renal fibrosis noninvasively to identify those patients who can benefit from antifibrotic therapy. In this review, we summarize recent advances in the assessment of renal fibrosis by magnetic resonance imaging.

Published by Elsevier Inc. on behalf of the National Kidney Foundation, Inc.

Key Words: Chronic kidney disease, Fibrosis, Magnetic resonance imaging, Fibroblast, Extracellular matrix

INTRODUCTION

CKD is a major cause of mortality and a serious global health challenge.¹ The prevalence of CKD continues to rise worldwide.² Therefore, new strategies for diagnosis and treatment of CKD are much needed to reduce its morbidity and mortality. Renal fibrosis is a pathologic hallmark of CKD, which is manifested by extensive fibroblast activation. Activated fibroblasts produce a large amount of extracellular matrix resulting in destruction of renal parenchyma and progressive loss of kidney function.³⁻⁵ Clinical studies have shown that the degree of renal interstitial fibrosis strongly predicts the prognosis of CKD.⁶

Traditionally, activated fibroblasts are thought to arise from resident fibroblasts.^{7,8} Recently, compelling evidence indicates that bone marrow-derived fibroblast precursors contribute significantly to the population of activated fibroblasts and the development of renal fibrosis.⁹⁻¹² Bone marrow-derived fibroblast precursors termed fibrocytes express hematopoietic markers, such as CD45 and CD11b, and mesenchymal markers, such as platelet-derived growth factor receptor- β and vimentin.¹³⁻¹⁵ Recent studies have demonstrated that bone marrow-derived fibroblast precursors contribute substantially to pathogenesis of renal interstitial fibrosis.¹⁵⁻¹⁸

Kidney biopsy is currently considered the gold standard for the evaluation of renal fibrosis. However, this invasive procedure has inherent complications, such as pain or bleeding to major complications including death. Furthermore, kidney biopsy is limited by inevitable sampling error. Currently, there are no routine noninvasive

assessments available for clinical diagnosis. Recent studies have shown that magnetic resonance imaging (MRI) may have clinical utility for noninvasive diagnosis of renal fibrosis.

Mechanisms of Renal Fibrosis

In response to kidney injury, multiple cell types in the circulation are recruited to the site of injury to participate in a wound healing response. A dysregulated wound healing process causes renal fibrosis, where extracellular matrix and fibroblasts replace normal renal parenchyma leading to kidney dysfunction. Fibrosis is a complex and progressive pathologic process. This involves infiltration of mononuclear cells including monocytes and immune cells. The interaction and communication among these cell types are involved in the pathogenesis of fibrotic disorders.^{19,20} Because fibroblasts are the principal effector cells that mediate extracellular matrix production in the fibrotic kidney disease, their activation is regarded as an important event in the pathogenesis of renal fibrosis.^{21,22} The activated fibroblasts are traditionally thought to arise from resident fibroblasts within the kidney. Recent studies have shown that these activated fibroblasts may originate from bone marrow-derived fibroblast precursors.^{16,23-27} Using bone marrow transplantation of transgenic mice that express GFP driven by collagen $\alpha 1(I)$ promoter, we have shown that bone marrow-derived hematopoietic fibroblasts migrate into the kidney, proliferate, and differentiate into myofibroblasts in an experimental model of obstructive nephropathy.^{16,18}

The recruitment of circulating fibroblast precursors into the sites of injury is mediated by chemokines generated in the local microenvironment. The chemokine CXCL16 is induced in the kidney after obstructive injury.^{16,28} We have used CXCL16 knockout mice to study the functional role of CXCL16 in the pathogenesis of renal fibrosis. CXCL16 knockout mice accumulate fewer bone marrow-derived fibroblast precursor and myofibroblast and displayed less extracellular matrix protein deposition in the obstructed kidneys.¹⁶ These results indicate that CXCL16 promotes renal fibrosis by recruiting bone marrow-derived fibroblast precursors into the kidney in response to obstructive injury. We further examined the role of CXCL16 in angiotensin II (Ang II)-induced renal injury and fibrosis. Genetic deletion of CXCL16 protects

From the Selzman Institute for Kidney Health and Section of Nephrology, Department of Medicine, Baylor College of Medicine, Houston, TX; and Center for Translational Research on Inflammatory Diseases (CTRID) and Renal Section, Michael E. DeBakey Veterans Affairs Medical Center, Houston, TX.

Support: See Acknowledgments on page 152.

Financial Disclosure: See Acknowledgments on page 152.

Address correspondence to Yanlin Wang, MD, PhD, Selzman Institute for Kidney Health, Department of Medicine-Nephrology, Baylor College of Medicine, One Baylor Plaza, BCM395, Houston, TX 77030. E-mail: yanlinw@bcm.edu

Published by Elsevier Inc. on behalf of the National Kidney Foundation, Inc. 1548-5595/\$36.00

<http://dx.doi.org/10.1053/j.ackd.2017.03.005>

the kidney from renal dysfunction, inhibits renal fibrosis, reduces proteinuria, suppresses bone marrow-derived fibroblast accumulation, myofibroblast formation, macrophage and T cell infiltration, and pro-inflammatory cytokine expression with no effect on Ang II-induced hypertension.²⁹ More recently, we have shown that CXCL16 plays a crucial role in the development of kidney fibrosis induced by deoxycorticosterone acetate/salt and renal artery stenosis.^{30,31}

CXCR6 is the CXCL16 receptor. We have recently shown that both circulating fibroblast precursors and bone marrow-derived fibroblasts in the kidney express CXCR6.^{16,18} We further demonstrate that genetic disruption of CXCR6 reduces the recruitment of bone marrow-derived fibroblast precursors into the kidney and the development of renal fibrosis induced by ureteral obstruction, ischemia-reperfusion, and Ang II-induced hypertension.^{17,18}

The activation of bone marrow-derived fibroblasts is modulated by inflammatory cells in the local microenvironment. T cells play an important role in the development of renal fibrosis,³² which have been shown to promote fibrocyte activation.¹² Naive CD4⁺ T cells can differentiate into 2 major distinct phenotypes, Th1 and Th2 cells, which are characterized by specific patterns of cytokine expression.³³ Th2 cells release Th2 cytokines, such as IL-4 and IL-13, to induce alternative activation of macrophage and promotes monocyte-to-fibroblast transition.^{33,34} Th1 cells generate Th1 cytokines, such as IFN- γ and IL-12, which promote classical activation of macrophages and inhibit fibrocyte differentiation.^{33,34} However, the molecular signaling mechanisms by which Th2 cytokines stimulate bone marrow-derived fibroblast activation are not well understood. We have recently shown that JAK3/STAT6 signaling stimulates bone marrow-derived fibroblast activation and extracellular matrix protein production.¹⁵ Pharmacologic inhibition of JAK3 with CP 690550 or genetic deletion of STAT6 suppresses myeloid fibroblast activation and inhibits development of renal fibrosis.¹⁵

Adiponectin is a multifunctional cytokine that regulates metabolism and inflammation. Recent evidence indicates that adiponectin levels in the circulation are elevated in patients with CKD, and a high level of adiponectin is linked to increased mortality.³⁵⁻³⁹ We have discovered that adiponectin is induced in the kidney after ischemia-reperfusion and obstructive injury.¹¹ Genetic disruption of adiponectin inhibits bone marrow-derived fibroblast accumulation and myofibroblast activation, which is associated with a reduction in the expression of profibrotic chemokines and cytokines and the production of extracellular matrix proteins in the injured kidneys after ureteral obstruction or ischemia-reperfusion. These results indicate that adiponectin promotes activation and maturation of myeloid fibroblasts and the development of renal fibrosis.

Furthermore, we have shown for the first time that alternatively activated (M2) macrophages produce collagen I, suggesting a link between M2 macrophage polarization and myeloid fibroblast activation.¹¹ Consistent with this novel concept, adiponectin deficiency reduces the number of procollagen-expressing M2 macrophages in the kidney after ureteral obstruction or ischemia-reperfusion injury.¹¹

These studies demonstrate that bone marrow-derived fibroblasts contribute significantly to the development of renal fibrosis. The recruitment and activation of bone marrow-derived fibroblasts are mediated by the interactions between locally produced chemokines and cytokines in the microenvironment. Therefore, targeting the signaling machinery of these chemokines and cytokines represents novel therapeutic strategy for fibrotic kidney disease.

Diagnosis of Renal Fibrosis

Kidney biopsy is the gold standard for the detection and diagnosis of renal fibrosis. However, there are several limitations of kidney biopsy including sampling error, intra- and inter-observer variability, and life-threatening complications.⁴⁰ Several biological molecules have been proposed as biomarkers for kidney fibrosis, but none of them have been validated and used clinically.⁴¹ Recent

advances in MRI techniques may allow accurate assessment and longitudinal evaluation of renal fibrosis. Two promising MRI techniques for assessing kidney fibrosis are diffusion-weighted MRI (DWI) and magnetic resonance elastography (MRE). The use of gadolinium-containing MRI contrast agents in patients with

advanced CKD is associated with nephrogenic systemic fibrosis, which is mediated by bone marrow-derived fibrocytes.^{42,43} Fortunately, both DWI and MRE do not require gadolinium-containing MRI contrast agents for the assessment of renal fibrosis.

DWI is an imaging technique that uses the diffusion of water molecules to generate contrast in MR images.⁴⁴ This technique allows noninvasively mapping the water movement in biological tissues *in vivo*. The commonly used parameter to quantify DWI is apparent diffusion coefficient (ADC) value. ADC is calculated by filtering signaling intensities from a series of DWI with different diffusion weightings (*b* values).

DWI has been used to evaluate renal fibrosis in patients with CKD. In a clinical study, Inoue and colleagues⁴⁵ used DWI to detect renal fibrosis *in vivo* in 142 patients with varying degree of kidney dysfunction. Healthy volunteers were recruited as controls. ADC values were significantly lower than healthy controls. Kidney biopsy was performed in a subset of CKD patients and kidney sections where the degree of renal fibrosis was evaluated morphologically by Masson's trichrome staining. The percentage of fibrotic area relative to the cross-section area in

CLINICAL SUMMARY

- Recent advances in magnetic resonance imaging (MRI) techniques may provide accurate assessment and longitudinal evaluation of renal fibrosis.
- Diffusion-weighted MRI (DWI) and MR elastography (MRE) are two most promising MRI techniques for assessing kidney fibrosis.

Download English Version:

<https://daneshyari.com/en/article/5685233>

Download Persian Version:

<https://daneshyari.com/article/5685233>

[Daneshyari.com](https://daneshyari.com)