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COMMENTARY

Possible therapeutic impact of the iron chelation on renal fibrosis

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Chronic kidney disease (CKD) patients are reportedly increasing in number worldwide and exhibit a significantly enhanced risk of cardiovascular complications. In addition, these patients also have an increased risk of CKD progression to end-stage renal disease, which requires hemodialysis or renal transplantation therapy.[1] There is increasing evidence of interorgan cross talk mediated by a variety of factors that may accelerate pathologic processes and the progression of organ dysfunction in the renal and cardiovascular systems.[2] In the kidney, the process of tubulointerstitial fibrosis is characterized by extracellular matrix deposition, interstitial myofibroblast proliferation and the infiltration of inflammatory mononuclear cells, which are thought to have an important role in the pathogenesis of CKD.[3] Therefore, amelioration of renal interstitial fibrosis is important to halt the progression of CKD.

Although iron is an elementary trace metal that is essential for viability in most organisms, excess iron can lead to Fenton/Haber–Weiss catalytic reactions and the generation of free radicals that are damaging to lipid membranes, proteins and nucleic acids, and cause organ damage. Thus, to maintain normal physiological tissue function, it is critically important to control the levels of circulating iron and tissue iron stores by sophisticated functional modulation of iron transporters and iron-binding proteins.[4]

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Naito *et al.*[5] are continuously investigating putative roles of iron in the pathogenesis of chronic kidney disease (CKD) by employing a rat model of CKD that uses 5/6 nephrectomy in Sprague–Dawley rats, which exhibit hypertension, glomerulosclerosis and renal interstitial fibrosis. Naito *et al.*[5] previously reported that renal iron accumulation and the expression of intracellular iron transport proteins were increased in the tubules of this CKD model. These authors also examined the effect of dietary iron restriction on renal damage and mineralocorticoid receptor signaling in this model and showed that dietary iron restriction ameliorated the development of renal damage and hypertension by inhibiting renal mineralocorticoid receptor signaling. In addition, Naito *et al.*[5] investigated the therapeutic effects of iron restriction on pre-existing hypertension and renal damage in the same rat model of CKD and showed that iron restriction prevented further deterioration of pre-existing renal damage through a similar inhibition of renal mineralocorticoid receptor signaling.[6] They also show that dietary iron restriction attenuated the development of hypertension and renal injury in aldosterone/salt-induced hypertensive mice.[7]

In this issue, Naito *et al.* further extend their above-mentioned studies and examine the effects of an oral iron chelator, deferasirox (DFX), on renal fibrotic lesion development in the 5/6 nephrectomy rat model of CKD.[8] In contrast to the inhibitory effect of dietary iron restriction on the development of hypertension and glomerulosclerosis in the CKD rat model, iron chelation by DFX did not affect hypertension or glomerulosclerosis. However, iron chelation by DFX did suppress fibrotic and inflammatory responses in the rats despite DFX treatment having no obvious effects on BP or the development of glomerular lesions.[8]

This is an important finding because renal interstitial fibrosis increases nocturnal BP, which contributes to a pathological diurnal BP rhythm and promotes renal deterioration in CKD patients.[9] In addition, renal interstitial fibrosis is a common feature of various types of end-stage renal disease. DFX treatment inhibited the upregulation of the renal expression of lipocalin 2, an important stimulator of renal fibrosis.[8] In addition, the transforming growth factor β (TGF-β) pathway (TGF-β and Smad3) is known to be involved in the pathogenesis of fibrotic lesions in the kidney,[10] and the oxidative-carbonyl stress pathway, including nicotinamide adenine dinucleotide phosphate oxidase that is suggested to be involved in the pathophysiology of renal fibrosis as well as the development of hypertension.[11,12] In this issue, Naito *et al.* demonstrated that iron chelation by DFX inhibits these fibrosis-, oxidative stress- and inflammation-related genetic changes in the kidney.[8]

Collectively, the authors suggest that iron chelation may be a therapeutic strategy for the inhibition of renal fibrosis in CKD. However, iron chelation with DFX did not affect proteinuria, glomerulosclerosis or podocyte injury associated with decreased renal intestinal fibrosis in CKD rats in the present study.[8] Therefore, as described by the authors, the attenuation of renal interstitial fibrosis by iron chelation may be a secondary effect that does not contribute to the mitigation of renal damage itself. Nevertheless, the results are interesting for understanding the pathophysiology of renal fibrosis in CKD. Recently, Ikeda *et al.*[13] showed that iron chelation by DFX prevents renal tubulointerstitial fibrosis in mice with surgically induced

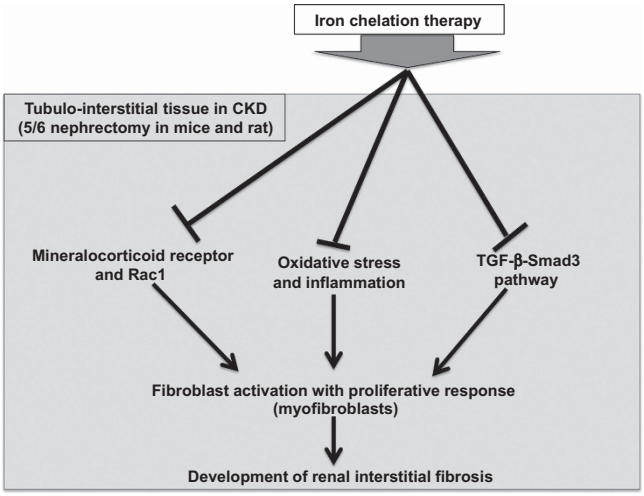

Figure 1 Schematic representation of the possible mechanism by which iron chelation ameliorates renal interstitial fibrosis in the 5/6 nephrectomy CKD (chronic kidney disease) model.

unilateral ureter obstruction by regulating TGF-β-Smad signaling, oxidative stress and inflammatory responses. Therefore, iron chelation is emerging as a possible target of interest for the efficient treatment of renal interstitial fibrosis (Figure 1). Further experimental and clinical evidence are needed to determine the exact effects of iron chelation.[14]

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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