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Matrix Metalloproteinase 2 is crucial for hypertension- and hyperglycemia-induced kidney injury independent of blood pressure

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In the United States, kidney diseases are a leading cause of death. According to the Center for Disease Control and Prevention, approximately 37 million US adults are estimated to have chronic kidney disease (CKD). Diabetes and high blood pressure are the leading causes of kidney failure, accounting for 3 out of 4 new cases. Primary preventions, like glycemic control, control of blood pressure, and lifestyle modifications, have shown promising benefits. However, very few drugs are available to retard CKD progression, despite extensive basic and clinical research.

Matrix metalloproteinases (MMPs) are a family of zinc-dependent enzymes that cleave the various components of extracellular matrix (ECM) (1). Because of their wide spectrum of activities and expression sites, MMPs are now acknowledged as key players in the regulation of both cell–cell and cell–extracellular matrix interactions in tissue repair and remodeling in response to injury and the progression of diseases (2). In this issue of the Journal, Hirata et al. (3) shed new light on the potential therapeutic significance of MMP-2 in CKD. This study examined the role of MMP-2 in the development of kidney injury in salt-sensitive hypertension and type 1 diabetes using the Dahl salt-sensitive (SS) rats. To examine the role of MMP-2 on kidney injury, an MMP-2 knockout rat strain was generated using ZFN technology on the SS genetic background. The authors took a complex approach to determine the contribution of MMP2 knockout in the setting of both hypertension- and hyperglycemic-induced nephropathy.

The SS rats developed hypertension, proteinuria, and marked renal injury in response to a high salt diet, as previously described. The renal expression and urinary excretion of MMP2 increased significantly in the SS rats. Deletion of MMP-2 from the SS rats substantially reduced kidney injury measured by proteinuria, glomerulosclerosis, fibrosis, and podocyte injury, when fed a high salt diet, which were at similar levels to the SS rats fed a low salt diet. Then, an STZ-induced diabetic model in the SS rats was tested.

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The main advantage of STZ-treated SS rats compared to other STZ-treated salt-resistant rodents is that STZ-SS rats not only develop type 1 diabetes, but also have profound kidney injury (4, 5). The SS rats treated with STZ developed proteinuria and renal injury along with significantly increased renal expression and urinary excretion of MMP2, similar to SS rats fed a high salt diet. STZ-treated MMP-2 KO rats exhibited a significant reduction in proteinuria and the excretion of nephrin and podocalyxin in comparison with STZ-treated SS rats. Deletion of MMP-2 significantly improved glomerulus permeability in STZ-treated MMP2 KO rats compared with STZ-treated SS rats. This study provided strong evidence for the pivotal role of MMP-2 in developing kidney injury in salt-sensitive hypertension and diabetes. Interestingly, these beneficial effects of MMP2 are independent of blood pressure, since deletion of MMP-2 had no significant effect on blood pressure in the MMP-2 KO rats fed a high salt diet or treated with STZ.

This manuscript is part of an ongoing effort from the same group exploring the significance and mechanisms of MMPs in hypertension and kidney injury. In previous studies, MMP2 was found to increase in hypertensive and diabetic animal models. Thus, broad-spectrum MMP inhibitors XL-784 and XL081 reduced proteinuria and kidney fibrosis in hypertensive SS rats and type 2 diabetic nephropathy (T2DN) rats (6). Novel MMPS inhibitors with increased selectivity and reduced toxicity have become available (1), and their therapeutic potential should be explored in additional animal and preclinical studies. The current study further identified the MMP2 isoform as a key player for kidney injury. Interestingly, no major changes in kidney function were observed in the MMP-2 KO rats without hypertensive or diabetic stress, which might be due to compensation by other MMPs. As reported previously, several MMPs, including MMP7 and MMP9, can be dysregulated in CKD (1). As an example, human kidney tissue proteomics recently identified MMP7 as a biomarker of fibrosis and kidney function decline (7).

Appropriate animal model used in this study is one of the strengths. The SS genetic background is characterized by more susceptibility to kidney injury due to impaired renal autoregulation. Myogenic and tubuloglomerular feedback responses are the two primary components of renal autoregulation and are diminished in SS rats (8). The impaired renal autoregulation permits alterations of systemic blood pressure transmitting to the glomeruli, which elevates intraglomerular pressure and indues injury (9). This could be one of the reasons that inconsistent observations were reported in MMP2 KO mice (10) since some mouse strains are very resistant to the development of hypertensive and diabetic kidney injury.

There are several open questions that need to be explored in future studies. First, the mechanisms have not been clarified for the elevation of MMP2 expression during hypertension, diabetes, and kidney injury. How MMP2 deletion protects against the development of kidney injury in hypertension and diabetes remains to be determined. In addition, MMP2 is expressed in many tissues and cell types. It is not clear how important MMP2 is in the kidney vs. other organs in the development of kidney injury since a global MMP2 deletion strain was used in this study. Results from this study and potential continuous future studies may provide a novel and effective therapeutic approach with selective MMP2 inhibitors for CKD patients with hypertension or diabetes.

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