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Proximal tubule specific Sirt6 has protective roles in UUO-induced renal tubulointerstitial fibrosis.

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Objectives: Renal fibrosis is a common feature of all progressive chronic kidney diseases. Sirt6 is a chromatin regulatory protein in the Sirtuin family of NAD⁺-dependent enzymes. Sirt6 has diverse roles in aging, metabolism, and disease. This study investigates the effect of proximal tubule specific Sirt6 knock-down on unilateral ureteral obstruction-induced renal tubulointerstitial fibrosis.

Methods: Renal fibrosis was induced by unilateral ureteral obstruction (UUO) in the wild type and γ GT⁽⁺⁾; *Sirt6*^{fl/fl} mice for 7 days. Histologic examination and Western blot analysis for α -SMA, type I collagen were performed. We also evaluated cell adhesion molecule expression after ureteral obstruction.

Results: We generated mice with conditional knockout of Sirt6 in renal proximal tubule epithelial cells by combining floxed *Sirt6* and *Cre* recombinase under the control of gamma-glutamyl transferase promoter. This proximal tubule specific Sirt6 knockout mouse shows decrease expression of Sirt6 after immunofluorescence staining after 1 week of ureteral obstruction. Renal tubular injury and fibrosis were increased after ureteral obstruction in γ GT⁽⁺⁾; *Sirt6*^{fl/fl} mice compared to wild type. The number of α -SMA positive fibroblasts and F4/80 positive macrophages were significantly increased after ureteral obstruction in γ GT⁽⁺⁾; *Sirt6*^{fl/fl} mice. In Western blot analysis, α -SMA, type I collagen, and intercellular adhesion molecule (ICAM)-1 expression was increased after ureteral obstruction in γ GT⁽⁺⁾; *Sirt6*^{fl/fl} mice.

Conclusions: These results suggest that proximal tubule specific Sirt6 has protective roles in UUO-induced renal fibrosis.