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Role of insulin-like growth factor binding protein 3 - sphingosine kinase 1 pathway in renal tubulointerstitial fibrosis

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Objectives : Renal tubulointerstitial fibrosis is a major final manifestation of chronic kidney disease and is associated with disease progression. Previous studies have demonstrated that insulin-like growth factor binding protein 3 (IGFBP3) was implicated with various fibrotic diseases. However, the role of IGFBP3 on the pathogenesis of renal fibrosis has not been fully investigated. Therefore, in the present study, the effect of IGFBP3 on renal tubulointerstitial fibrosis via sphingosine kinase 1 (SphK1) pathway was explored in unilateral ureteral obstruction (UUO) animals and tumor growth factor-ß1 (TGF- ß1) treated renal tubular cells.

Methods : In vivo, UUO was performed in Sprague-Dawley rats (n=12). The kidney were harvested after 10 days of UUO. Immunohistochemistry was conducted with renal tissues. In vitro, renal proximal tubular cell (NRK-52E) was cultured in DMEM media containing 25 mM glucose (control) or recombinant TGF-ß1 (10 ng/mL) with or without IGFBP3 siRNA transfection. To evaluate the interaction between IGFBP3 and SphK1, the effect of IGFBP3 siRNA and SphK1 siRNA was also examined in TGF-ß1 treated NRK-52E cell. Real-time PCR and Western blot analysis were performed to evaluate IGFBP3, SphK1, fibronectin, collagen type 1, and α-smooth muscle actin (α-SMA).

Results : In UUO rats, immunohistochemistry showed that kidney IGFBP3 expression was significantly up-regulated, compared to controls. The mRNA and protein expression of IGFBP3 were significantly higher in recombinant TGF-ß1 treated NRK-52E cells, compared to control cells. Protein expression of fibrosis-related proteins including fibronectin, collagen type 1, and α-SMA were significantly increased in TGF-ß1 stimulated cells. Increased expression of fibrosis-related proteins were significantly attenuated by IGFBP3 siRNA transfection in cells treated with TGF-ß1. Furthermore, IGFBP-3 siRNA transfection reduced the increase in SphK1 expression induced by TGF-ß1 treatment, but SphK1 siRNA transfection did not change the expression of IGFBP3 in NRK-52E cells.

Conclusions : These results suggest that IGFBP3 may be a significant mediator in renal tubulointerstitial fibrosis via 'IGFBP3-SphK1' signaling pathway.

Keywords : IGFBP3; Sphingosine kinase 1; Renal tubulointerstitial fibrosis; NRK-52E