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Autophagy in FOXD1 stroma-derived cells plays a critical role in renal tubulointerstitial fibrosis

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Objectives : Renal fibrosis is the final common pathway of various renal injuries and it leads to chronic kidney disease. FOXD1+ progenitors give rise to an extensive population of stromal cell, which mature to form vascular smooth cell, glomerular mesangial cells and pericytes. FOXD1 lineage pericyte plays a critical role in renal tubulointerstitial fibrosis (TIF). Autophagy is a cellular process of degradation of damaged cytoplasmic components and regulates cell death and proliferation. In this study, we investigated the role of autophagy in FOXD1 stroma-derived cells on renal TIF using conditional knockout mice in which Atg7 was genetically ablated specifically in FOXD1 stroma-derived cells.

Methods : We generated conditional knockout mice in which Atg7 is genetically ablated specifically in FOXD1-cells (Atg7flox/flox;FOXD1-Cre+) and performed unilateral ureteral obstruction (UUO). Atg7flox/flox litermates served as controls.

Results : Extracellular matrix deposition and the protein expression of TGF-β and α-smooth muscle antibody were substantially increased in the obstructed kidneys of Atg7flox/flox;FOXD1-Cre+ mice after UUO with those of WT mice. Terminal deoxynucleotidyl transferase dUTP nick end labeling (TUNEL) assay revealed that the number of TUNEL-positive cells was significantly greater in obstructed kidneys of in Atg7flox/flox;FOXD1-Cre+ compared with WT mice after UUO. TUNEL-positive cells were co-localized with PDGFR-β and tubular cell markers. The protein expression of C-myc was substantially increased in the obstructed kidneys of Atg7flox/flox;FOXD1-Cre+ mice.

Conclusions : Our data showed that autophagy in FOXD1 stroma-derived cells play a protective role in development of renal TIF and apoptosis of stromal cell as well as tubular epithelial cells, which may be a new therapeutic target for

renal TIF.

Keywords : autophagy, kidney, fibrosis, apoptosis