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Deletion of Akt1 contributes to renal fibrosis in murine model of unilateral ureteral obstruction

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Objectives: Previous studies have found the increased Akt activity in experimental renal fibrosis. We investigated the role of Akt1, one of the three Akt isoforms, in renal fibrosis using the murine model of unilateral ureteral obstruction (UUO).

Methods: In vivo, we subjected the wild type and *Akt1*$^{-/-}$ mice to UUO. In vitro, gene silencing of Akt1 was achieved using the short hairpin RNA delivered by the lentiviral vector in immortalized human proximal tubular cells (HK2 cells) and rat kidney fibroblasts (NRK-49F cells).

Results: In immunohistochemical stain, the expression of Akt1 was significantly higher in obstructed kidneys of wild type mice compared with control sham kidneys and increased gradually as UUO progressed. The fibronectin, type I collagen, and heat shock protein 47 (HSP47) were markedly more expressed in obstructed kidneys of *Akt1*$^{-/-}$ mice than in those of the wild type mice. Transforming growth factor β1 (TGFβ1) was highly induced within 1 day of UUO in obstructed kidneys of *Akt1*$^{-/-}$ mice and the expression of TGFβ1 was significantly higher in the *Akt1*$^{-/-}$ mice than in the wild type mice as UUO progressed. Western blot showed that the silencing of Akt1 increased the expression of TGFβ1, which was enhanced by angiotensin II stimulation in HK2 cells, but not in NRK-49F cells. Immunohistochemical stain demonstrated that the expression of cleaved caspase-3 in renal tubules was significantly higher in the *Akt1*$^{-/-}$ mice than in the wild type mice. Western blot showed that the silencing of Akt1 increased the expression of cleaved caspase-3 in HK2 cells, but not in NRK-49F cells.

Conclusions: Our findings suggest that the deletion of Akt1 might contribute to tubulointerstitial fibrosis and tubular apoptosis via TGFβ1 induction. We also showed that TGFβ1 upregulation by genetic deletion of Akt1 is associated with activation of STAT3 independently of the TGFβ1/Smad signaling pathway.