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Akt1 is involved in renal fibrosis and tubular apoptosis in a murine model of acute kidney injury-to-chronic kidney disease transition

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Objectives: Maladaptive repair after acute kidney injury (AKI) can predispose patients to chronic kidney disease (CKD). However, the molecular mechanism underlying the AKI-to-CKD transition remains unclear. The Akt signaling pathway has been reported to be involved in the pathological processes of both AKI and CKD. In this study, we investigated the role of Akt1 in a murine model of the AKI-to-CKD transition.

Methods: Wild-type (WT) and *Akt1*$^{-/-}$ mice were subjected to unilateral ischemia-reperfusion injury (UIRI), with their kidneys harvested after two days and two, four, and six weeks after UIRI. The dynamic changes in tubulointerstitial fibrosis, markers of tubular epithelial-mesenchymal transition (EMT), and tubular apoptosis were investigated.

Results: Akt1 of the three Akt isoforms was activated during the AKI-to-CKD transition. After UIRI, tubulointerstitial fibrosis and tubular EMT were significantly increased in WT mice, but were attenuated in *Akt1*$^{-/-}$ mice. The expression of the transforming growth factor (TGF)-β1/Smad was increased in both WT and *Akt1*$^{-/-}$ mice, but was not different between the two groups. The levels of phosphorylated glycogen synthase kinase (GSK)-3β, Snail, and β-catenin in the *Akt1*$^{-/-}$ mice were lower than those in the WT mice. The number of TdT-mediated dUTP nick-end labeling (TUNEL)-positive tubular cells and the expression of cleaved caspase-3/Bax were both lower in *Akt1*$^{-/-}$ mice than in WT mice.

Conclusions: Genetic deletion of *Akt1* was associated with attenuation of tubulointerstitial fibrosis, tubular EMT, and tubular apoptosis during the AKI-to-CKD transition. These findings were associated with Akt1/GSK-3β/ (Snail and β-catenin) signaling independent of TGF-β1/Smad signaling. Thus, Akt1 signaling could serve as a potential therapeutic target for inhibiting the AKI-to-CKD transition.