

KSN 2017 Abstract

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Diabetes Aggravate Post-ischemic Renal Fibrosis through Persistent Activation of Shh Signaling.

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Objectives : Diabetes has a high risk for chronic kidney disease (CKD) and increases the severity of acute kidney injury (AKI). AKI induces renal fibrosis, known as a key feature of CKD, and renal fibrosis is associated with transforming growth factor- β 1 (TGF- β 1) and sonic hedgehog (Shh) signaling pathway. However, it is not known whether diabetes accelerates CKD progression via Shh signaling after AKI. Here, we investigated the influence of diabetes on CKD progression after AKI.

Methods : We established unilateral renal ischemia-reperfusion injury (IRI) model in streptozotocin induced diabetic mice. Histological changes in the kidney were evaluated at 3 and 5 weeks after IRI. The expression levels of mRNAs and proteins related to fibrosis and inflammation were determined by qRT-PCR and western blot. The effect of hyperglycemia on the epithelial-mesenchymal transition (EMT) induced by TGF- β 1 and Shh signaling pathway was demonstrated in HKC-8.

Results : When comparing between 3 and 5 weeks after IRI, there was no improvement of tubulointerstitial injury in diabetes. Renal fibrosis was significantly higher in diabetes than in non-diabetes at 5 weeks after IRI. The pattern of infiltrated T and B cell was also consistent with that of renal fibrosis. The mRNA and protein expression levels of related TGF- β 1 and Shh signaling pathway were significantly higher in the diabetic IRI kidneys than in the non-diabetic IRI kidneys. In vitro, Hyperglycemia led to the expression levels of TGF- β 1 and Shh, and then interacted with each other for the progression of fibrosis.

Conclusions : Taken together, we demonstrated that diabetes on IRI induced

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the persistent activation of TGF- β 1 and Shh signaling pathway and aggravate the interstitial renal fibrosis. In addition, the susceptibility to TGF- β 1 and Shh was increased by hyperglycemia in renal tubular cells.

Keywords : Ischemia reperfusion injury, Diabetes, Fibrosis, Transforming growth factor- β 1, Sonic hedgehog