Deletion of Smad3 Prevents Renal Fibrosis and Inflammation in Type 2 Diabetes

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Objective: Transforming growth factor (TGF)-β/Smad signaling is highly activated in the diabetic kidney in patients with type-2 diabetes. However, the precise role of Smad3 in the pathogenesis of type-2 diabetic nephropathy remains largely unclear, which was investigated in this study by specifically deleting Smad3 from db/db mice.

Methods: Smad3 knockout (KO)-db/db mice were generated by crossing the Smad3 null allele on a db/db background. Treatment in db/db mice with shRNA targeting Smad3 was shown to reduce TGF-β expression and prevent renal fibrosis.

Results: Compared to Smad3+/db/m and Smad3+/db/m mice that exhibited normal levels of blood glucose and urinary albumin excretion over the 32-week time course, Smad3−/−/db/db, Smad3+/−/db/db, Smad3+/−/db/dm, and Smad3−/−/db/m mice. Groups of 8 mice were sacrificed at weeks 8, 20, and 32 and effect of deleting Smad3 gene on levels of fasting blood glucose, renal function, histological injury, and molecular pathology were examined.

Conclusion: Deletion of Smad3 prevents the development of type-2 diabetic nephropathy. This novel finding strongly suggests that targeting Smad3 may be a novel and effective therapy for type-2 diabetic complications clinically.
pollutants (POP) affects renal injury has not been elucidated. Perfluorooctane sulfonate (PFOS) is an emerging POP in China. PFOS is readily absorbed after oral exposure and accumulates primarily in the serum, kidney, and liver. Toxicological studies on animals indicate its potential developmental, reproductive and systematic effect. PFOS can activate peroxisome proliferator-activated receptor alpha (PPARalpha) and may act via PPARalpha to produce some of their effects. In this study, we examined whether PFOS enhanced renal injury in vitro under diabetic condition. Our results demonstrated that the presence of PFOS was able to enhance the expression of fibrotic markers and enhanced oxidative stress in renal tubular epithelial cells under diabetic condition. PFOS also promoted the apoptosis of the renal tubular epithelial cells. This study demonstrated that presence of PFOS promoted renal injury in vitro under diabetic condition, suggesting that an environmental pollutant is associated with renal injury in DN.

http://dx.doi.org/10.1016/j.hkjn.2015.08.014

0064
Hyperphosphatemia and Tubulointerstitial Injury in the Progression of Diabetic Nephropathy
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Objective: To evaluate the relationship between tubulointerstitial injury and hyperphosphatemia in the patients with type 2 diabetes and diabetic nephropathy (T2DN), and investigate the association of hyperphosphatemia with the renal outcome, especially in the T2DN patients with eGFR< 60 ml/min per 1.73 m².

Methods: A total of 396 patients with T2D and biopsy-proven DN from Nanjing DN registration system who received follow-up for at least 1 year were recruited and median 5-year follow-up. Renal outcomes were defined by progression to end-stage renal disease and doubling of serum creatinine.

Results: Of the participants, the baseline eGFR was 73.86 ± 33.52 mL/min per 1.73 m². The levels of the urinary tubulointerstitial injury markers including the NAG, RBP and NAGL were significantly difference among quintiles of serum phosphorus (P < 0.01). The participants whose eGFR < 90 mL/min per 1.73 m² had a higher rate of tubulointerstitial injury (interstitial fibrosis tubular atrophy scores of 2 and 3, P = 0.005; interstitial inflammation scores of 1 and 2, P = 0.035) in hyperphosphatemia (≥1.45 mmol/L) group than in lower phosphorus group (<1.17 mmol/L). Participants with baseline levels of serum phosphorus in higher quintiles had a higher cumulative incidence of ESRD (log-rank, P < 0.01). In the analyses adjusted by age, sex, diabetes status, BP, FBG, BMI, proteinuria, cholesterol, and eGFR, the relationship between higher serum phosphorus and an increased risk of ESRD remained. The association between serum phosphorus and ESRD risk persisted and was stronger when the sample was restricted to those with a baseline eGFR equal to 60–90 mL/min per 1.73 m², but not when it was restricted to patients with a baseline eGFR of 30–60 mL/min per 1.73 m².

Conclusion: These findings indicated the baseline serum phosphorus is associated with tubulointerstitial injury of T2DN. And serum phosphorus >1.45 mmol/L is an independent risk factor of ESRD in T2DN, especially in the patients with eGFR < 60 mL/min per 1.73 m².

http://dx.doi.org/10.1016/j.hkjn.2015.08.015

0072
Gene Expression Profile Analysis of Tangshen Formula-treated db/db Mice
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Objective: Tangshen formula (TSF), as a traditional Chinese medicine, has been shown to have good clinical efficacy in diabetic nephropathy (DN) treatment. In this study, the potential molecular targets of TSF were explored in db/db mice treated with TSF.

Methods: db/db mice were treated with or without TSF by gavage for 12 weeks, with db/m mice as a control. Serum glucose, 24h-albuminuria and histology were detected. Gene expression microarray was carried to detected the gene expression profile in 3 groups mice kidney tissues.

Results: The results showed that treatment with TSF significantly reduced serum glucose and the excretion of urinary albumin in db/db mice, and attenuated secretion of extracellular matrix in renal glomeruli. Clustering analysis indicated the three groups could be their respective together for a class and almost 400 differentially expressed genes were identified in db/db mice and TSF-treated mice. These genes were mainly involved in predicting long-term renal outcome is uncertain, particularly in the Type 2 diabetic nephropathy (DN).

Methods: A total of 501 patients (The National Clinical Research Center of Kidney Diseases, 2003–2011) were recruited in prospective cohort study. Follow-up was 5-year. Renal outcome was defined by eGFRcre-cys < 15 mL/min per 1.73 m² or renal replacement therapy.

Results: The distributions of standardized serum cystatin C with eGFRcre and eGFRcre-cys are shown in Figure 1. Kaplan-Meier curves showed significantly increased renal end points with higher quartile of cystatin C (p < 0.001) and lower eGFRcre-cys (p < 0.001). The highest AUROCs was eGFRcre-cys in predicting the renal endpoint compared with eGFRcre or eGFRcys. The best cut-off value for predicting the renal endpoint was 29.28% decline in the 24-month, which value showed 79.6% sensitivity and 82.6% specificity. Cox regression models with restricted cubic splines were shows a change of −30% in eGFRcre-cys was associated with adjusted HRs for ESRD of 27.92 (95%CI, 3.95–197.48) over 2-year.

Figure 1. The population of estimated GFRcre, GFRcys and GFRcre-cys equation.