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The Effect of Akt1 on Glomerulosclerosis of Nonobstructed Kidney : Unilateral Ureteral Obstruction Mice Model with Akt1 Deletion

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Objectives : Unilateral ureteral obstruction (UUO) model has been used for investigating the tubulointerstitial fibrosis and inflammation. The main pathogenic mechanism is related with systemic activation of renin angiotensin system and profibrotic factors, such as TGF-β and Smad pathway. Recently, in the context of glomeruli, sclerotic changes has been occurred in nonobstructed contralateral kidney rather than obstructed kidney. Although Akt signaling has considered to have an important role in chronic kidney disease, there is few report related the role of Akt1 in glomeruli of unilateral ureteral mice model. This study aimed to explore the changes of glomeruli according to obstructed time between Akt1 knock-out (Akt1-/-) mice and wild type mice.

Methods : Mice lacking Akt1 (Akt1-/-, C57BL/6. 129P2-Akt1tm1Mbb/J) mice and wild type mice (C57BL/6) were subjected to unilateral ureteral ligation and euthanized 1, 3, 7 days later, respectively. In both group, modified glomerulosclerosis index was applied and we compared the degree of glomerulosclerosis between obstructed and nonobstructed kidney according to genetic condition of Akt1. Also, rat mesangial cells (RMC) were used for in vitro experiment. TGF-β and angiotensin II were treated on RMC and compared the cellular signaling change between Akt1-/- and control cells.

Results : In vivo: The glomerulosclerosis of nonobstructed kidney is apparently prominent compared with that in obstructed kidney in the setting of Akt1-/-. However, in wild type, there is no statistically difference between obstructed and nonobstructed kidney in terms of glomerulosclerosis. In Akt1-/- mice, these glomerulosclerotic change was more prominent in 7 days compared with 1, 3 days UUO model. The glomerulosclerosis in nonobstructed kidney in Akt1-/- mice is more severe as compared to wild type mice mainly at 3, 7 days. However, the glomerulosclerosis in obstructed kidney is comparable to that in wild type.
In vitro: The ERK1/2 was highly activated more than 3 fold by TGFβ1 in RMC

with Akt1−/− as compared with control. The genetic deletion of Akt1 itself induced the expression of TGFβ1 as compared with control. The phosphorylation of Smad-2 was markedly lower in Akt1−/− as compared with control. The phosphorylation of Smad-3 was highly induced by TGFβ1 in Akt1−/− groups as compared with control. The ERK1/2 was highly activated more than 4 fold by AngII in two groups. There were no differences between two groups. The phosphorylation of Smad-3 was induced by AngII in Akt1−/− as compared with control.

Conclusions : Akt1 may affect the glomerulosclerosis in nonobstruced kidney of unilateral ureteral obstruction model. This finding might be ascribed to the filterable factors, which could be related with augmented glomerulosclerotic changes in the Akt1-deleted milieu. In terms of the mechanism, the response of MAPK/ERK and Smad pathway could be augmented by TGFβ1 and AngII in the setting of Akt1−/− .

Keywords : Akt, fibrosis, glomerulosclerosis, unilateral ureteral obstruction