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신장 세뇨관 상피세포의 Epithelial-mesenchymal Transition에 미치는 히스톤탈아세틸화 효소 2의 역할

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Histone Deacetylase 2 Plays an Important Role in Epithelial-Mesenchymal Transition of Renal Tubular Epithelial Cells

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Aim : Diabetic nephropathy is the leading cause of end- stage renal disease and characterized by excessive accumulation of extracellular matrix (ECM) in the kidney. The role of reactive oxygen species (ROS) and epithelial- mesenchymal transition (EMT) in the development of diabetic renal injury is well known. Previous studies showed that trichostatin A (TSA), a histone deacetylase (HDAC) inhibitor, prevented albuminuria, EMT, and enhanced ECM expression in streptozotocin (STZ)- induced diabetic rat kidney without significant effect on blood glucose. The exact role of HDAC in diabetic renal injury, however, remains incompletely understood. The purposes of our present study were to evaluate the relative role of each HDAC isoform in renal fibrosis and to determine the role of ROS in increased HDAC activity.

Methods : Normal rat kidney epithelial (NRK- 52E) cells were maintained in DMEM with 5% fetal bovine serum and antibiotics. Synchronized cells were stimulated by 10 ng TGF- β 1/mL and 200 μM H_2O_2 for 24 hr. N- acetylcystein (NAC) 10 mM were administrated 1 hr before the addition of TGF- β 1. Small interference RNA (siRNA) duplex HDAC2 was transfected by lipofectamine for 24 hr. The stealthTM universal negative control was used as a control. Kidneys of STZ- induced diabetic rats and db/db mice were also used. HDAC activity was measured by HDAC activity kit and fibronectin, α - SMA, and E- cadherin mRNA expression by RT- PCR.

Results : TGF- β 1 significantly increased activity, but not mRNA expression, of HDAC2 in NRK- 52E cells. The activities of HDAC1,3,4,5,8 were not altered by TGF- β 1. HDAC1,2,4 activity were increased in db/db mice kidneys and HDAC2,4 activity in STZ- induced diabetic rat kidneys. Silencing HDAC2 repressed TGF- β 1- induced fibronectin and α - SMA/E- cadherin upregulation in NRK52E cells. H_2O_2 also increased the activity of HDAC2, but not other isoforms, in NRK- 52E cells. Moreover TGF- β 1- induced HDAC2 activity was decreased by NAC, suggesting that H_2O_2 may directly activate HDAC2 in NRK- 52E cells.

Conclusion : These results demonstrate that HDAC2 plays an important role in the development and progression of renal fibrosis and that ROS mediate increased HDAC2 activity in NRK- 52E cells cultured under TGF- β 1. These data suggest HDAC2 as a novel therapeutic target for the attenuation of diabetic renal injury (This works was supported by R01- 2006- 000- 10829- 0 and R15- 2006- 020 from KOSEF and the second stage of Brain Korea 21 Project).

Key Words : 탈아세틸화효소, 세포변이, 활성산소종
HDAC, EMT, ROS