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신섬유화에서 조직 트랜스글루타미네이즈의 역할

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Tissue Transglutaminase Inhibitor Attenuates Interstitial Fibronectin Accumulation in vitro and in vivo

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Extracellular matrix (ECM) accumulation either in the glomerular mesangium or in the tubulointerstitium, plays a crucial role in destroying nephron structure and function, and finally results in renal fibrosis. Tissue transglutaminase (tTg) bind and cross- link ECM proteins in the ECM, especially fibronectin(FN), and the resultant ε - (γ - glutamyl) lysine bonds are stable and highly resistant to proteolytic degradation. We hypothesized that tTg might play an important role on the progress of renal fibrosis via cross- linking ECM proteins and tried to halt its progress by tTg inhibition in vitro and in vivo.Human renal proximal tubular epithelial cells (RPTEC) were treated with 5 ng/mL of rhTGF- β 1 and novel tTg inhibitor KCC009 was added to culture medium at final concentration of 100 uM in the attenuation group. After 72 hours of stimulation/attenuation, cells were harvested and fibronectin multimers and tTg activity were measured by immunoblotting. RNA extracted with TRIzol was reverse transcribed for quantitative PCR of tTg and MMPs. Tubulointerstitial fibrosis was induced by ligation of unilateral ureter of 6-week- old male C57Bl6 mice. In the treatment group, cystamine (11.2 mg/100 g mouse) was introduced by intraperitoneal injection daily. All mice (N=5 for each group:control; disease control;treatment group) were sacrificed at the 14th day of disease. Fibronectin multimers and tTg activity were measured by immnunoblotting, and interstitial fibrosis was measured by semiquantitative method.Fibronectin multimers increased with rhTGF- β 1 stimulation were attenuated with KCC009, and the decrease of fibronectin multimers was parallel with tTg activity which was measured by immunoblotting. Real time PCR of cDNA revealed upregulation of MMP2, MMP9 and tTg with rhTGF- β 1 stimulation. In UUO kidney, interstitial fibrosis were markedly increased. Although interstitial fibrosis score was not lowered after tTg inhibitor attenuation in semiquantitation analysis, fibronectin multimer deposition was decreased after tTg inhibitor treatment. We showed that tTg activity increased after the stimulation which triggers renal fibrosis and the increase of its activity was associated with the deposition of fibronectin multimers. Attenuation of fibronectin multimer formation by tTg inhibitor shown on this study leads to newer approach to halt the progression of renal fibrosis, and tTg might be considered as an attractive therapeutic target for renal fibrosis.

Key Words : 조직 트랜스글루타미네이즈 저해제, 신섬유화
Tissue transglutaminase inhibitor, Renal fibrosis