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신장섬유화 모델에서 히알루론산의한 림프관생성에서 신장상피세포에서 분비된 VEGF-C역할

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Hyaluronic Acid Increases Vascular Endothelial Cell Growth Factor-C from Proximal Tubular Cells

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Hyaluronic acid (HA) is one of important component of extracellular matrix proteoglycan, has many biologic and pathologic effects such as inflammation, angiogenensis, wound healing and tissue remodeling. Renal lymphangiogenesis has been demonstrated in a rat remnant kidney model and human transplanted kidney. However, there is few data about the effect of transforming growth factor (TGF) β-1 and HA on vascular endothelial cell growth factor (VEGF)-C expression in renal proximal tubular epithelial cells. We investigated the effect of TGF β1 and HA on VEGF-C production in renal proximal tubular epithelial cells.

Renal proximal tubular epithelial cells were incubated with TGF- β1 and HA production was evaluated by ELISA. VEGF-C expression in renal proximal tubular epithelial cells were evaluated by immunoblotting and VEGF-C expression in UUO-induced fibrotic kidney were examined with immunofluorescence.

TGF-b1 (1, 5, and 10 ng/mL) increased hyaluronic acid synthase (HAS)1, HAS2 and HAS3 mRNA expression in proximal tubular cells. ELISA data demonstrated that treatment of proximal tubular cells with TGF-β1 (10 ng/mL) increased HA production in a dose- and time-dependent manner. We also found that TGF receptor inhibitors (LY364947, SD208, and SB431542) significantly decreased TGF-β1-induced HA production. We next tested whether HA affects the expression of VEGF-C in proximal tubular cells. Western blot analysis revealed that HA increased VEGF-C expression in a dose- and time-dependent manner in proximal tubular cells. In UUO model, renal TFG β1 level was higher in ureteral obstruction operated kidney than that of sham-operated kidney. Our immunofluorescence finding showed that, HA is expressed on surface of proximal tubular epithelial cells in UUO kidney. VEGF-C expression was increased in aquaporin 1 (proximal tubular marker)-positive renal tubular cells 7 days after ureteral obstruction. Immunohistochemical staining revealed scanty expression of HA in the renal cortex, with the exception of papillae in sham-operated mice. In contrast, HA accumulation in the interstitial space of the renal cortex increased 1 and 2 w after UUO. HA accumulation is correlated with the number of LYVE-1-positive lymphatic vessels in the UUO kidney

These results suggest that TFG-β1 induces HA production and HA potentiates VEGF-C expression in proximal tubular epithelial cells in UUO-induced renal lymphangiogenesis.

Key Words: 림파관, 신장섬유화, 히알루론산
Lymphatics, Renal fibrosis, Hyaluronic acid