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만성 일측 요관 폐쇄성 신증 모델에서 대식세포와 신혈관의 혈관내피세포성장인자(VEGF-C)의 림프관신생

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Lymphangiogenesis via Vascular Endothelial Growth Factor-C from Macrophages and Renal Tubules in a Unilateral Ureteral Obstruction Mouse Model

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Lymphatic remodeling in inflammation has been demonstrated in tracheal myocoplasma infection, human kidney transplant, skin inflammation, peritonitis, and corneal inflammation. We investigated lymphangiogenesis in fibrotic area in a unilateral ureteral obstruction (UUO), a progressive renal fibrosis model and evaluated the roles of macrophages and renal tubules as a source of vascular endothelial cell growth factor (VEGF)-C in obstructed kidney. Our results demonstrated that density of LYVE-1-positive lymphatic vessels was increased after ureteral obstruction, and LYVE-1-positive lymphatic vascular density was correlated with the progression of interstitial fibrosis. LYVE-1-positive lymphatic endothelial cells were colocalized with podoplanin, Prox-1, and VEGF receptor-3 in fibrotic kidney. Proliferation of LYVE-1-positive lymphatic endothelial cells was increased after UUO compared to sham-operated mice kidney. VEGF-C mRNA expression was significantly increased after UUO compared to the sham-operated mice kidney whereas angiopoietin-2, VEGF-B, and VEGF-D mRNA expression was not changed. Depletion of macrophages with clodronate decreased lymphangiogenesis in UUO kidney. VEGF-C expression in M2-polarized macrophages was higher than M1-polarized macrophages from bone marrow-derived macrophages, and VEGF-C expression was also increased in Raw 264.7 cells, an established macrophage cell line, by stimulation with TGF-β1 or TNF-α. Stimulation of MPT and HK2 cells with TGF-β1 or TNF-α increased the expression of VEGF-C. The density of D2-40-positive lymphatics in obstructed human kidney due to ureteral cancer was increased compared to normal kidney. These results indicate that VEGF-C from macrophages and renal tubules is associated with lymphangiogenesis in fibrotic kidney in UUO mouse model.

Key Words: 만성일측요관폐쇄신증, 림프관신생, 대식세포
Unilateral ureteral obstruction, Lymphangiogenesis, Macrophage