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Hyaluronic Acid Induces Lymphangiogenesis in Mouse Unilateral Ureteral Obstruction Model via Stimulation of Macrophage VEGF-C Production

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Hyaluronic acid (HA) is one of important component of extracellular matrix proteoglycan. HA level is increased in chronic inflammation and has many biologic and pathologic effects such as inflammation, angiogenensis, wound healing and tissue remodeling. Our group reported that VEGF-C and VEGF-D from macrophages and tubular cells had induced lymphangiogenesis in mouse unilateral ureteral obstruction (UUO) model. However, there is few data about the effect of HA on lymphangiogenesis in renal fibrosis. To elucidate the role of HA in UUO-induced lymphangiogenesis, we investigated the expression of HA in UUO-induced lymphangiogenesis and the effect of HA on VEGF-C production in macrophages.

Methods: In vitro lymphangiogenic effects of HA in human lymphatic endothelial cells (hLECs) and >in vivo effect of HA on VEGF-C expression in UUO-induced lymphangiogenesis were evaluated.

Results: In UUO kidney, HA expression was increased in tubulointerstitial area 7 d after UUO. The density of LYVE-1-positive lymphatic endothelial cells was significantly increased in cortical interstitial fibrotic areas. HA expression correlates with lymphangiogenesis in UUO. VEGF-C expression was increased and F4/80-positive cells are costained with VEGF-C in kidney section after 1 w of UUO. About 35% of F4/80-positive macrophages was co-stained by HA and macrophage depletion with clodronate significantly decreased UUO-induced lymphangiogenesis. Our results also showed that low molecular weight HA induced capillary-like tube formation in the hLECs and treatment of HA in bone marrow derive marcrophages increased the expression of VEGF-C in a dose- and time-dependent manner.

Conclusions: These results suggest that HA has a lymphangiogenesis effects in UUO-induced renal fibrosis via stimulation of VEGF-C production in macrophages.

Key Words: 만성신질환, 대식세포, 림프혈관신생
Renal fibrosis, Macrophage, Lymphangiogenesis