KSN 2017 Abstract

Lymphangiogeneis in the kidney diseases and hypertension

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An important function of lymphatic vessels is the regulation of fluid in interstitial space and transport of immune cell and nutrients. Lymphangiogenesis is associated with many pathological conditions such as tumor metastasis, wound healing, lymphedema, acute inflammatory conditions and fibrosis. Vascular endothelial growth factor (VEGF)-C and VEGF-D are important lymphangiogenic factors and their receptors are VEGFR-2 (Flk-1/KDF) and VEGFR3 (Flt-4). Lymphatic endothelial cell markers are introduced: lymphatic vessel endothelial hyaluronan receptor-1 (LYVE-1), podoplanin, prox-1 and vascular endothelial growth factor receptor 3 (VEGFR3). Therefore, there is a growing body of evidence about the relationship between lymphangiogenesis and kidney disease or hypertension.

There is lymphangiogenesis in fibrotic renal area in a unilateral ureteral obstruction model. Compared to sham-operated mice, the number of LYVE-1-positive lymphatic vessels, the proliferation of LYVE-1-positive lymphatic endothelial cells, along with VEGF-C and -D mRNA expression were all significantly increased following ureteral obstruction. Depletion of macrophages with clodronate decreased lymphangiogenesis in the obstructed kidney. VEGF-C expression increased in macrophages by stimulation with TGF-β1 or TNF-α. Additionally, the blockade of VEGF-C and VEGF-D signaling decreased obstruction-induced lymphangiogenesis. Thus, VEGF-C and VEGF-D are associated with lymphangiogenesis in the fibrotic kidney and macrophage is an important source of VEGF-C and VEGF-D in a mouse model of ureteral obstruction.

Hyaluronan (HA), a component of the extracellular matrix, is a new lymphangiogenic factor in kidney fibrosis. HA cooperated synergistically with vascular endothelial cell growth factor-C to stimulate capillary-like tube formation and increase migration of LECs. Accumulation of HA in the cortex was positively correlated with the lymphangiogenesis after UUO. Additionally, transfer of mHAS2 and mHAS3 knock-down CD11b-positive macrophages to SCID mice resulted in a partial decrease in UUO-induced lymphangiogenesis. HA increased expression of VEGF-C in macrophages. VEGF-C expression and LYVE-1-positive lymphatic area was significantly lower in the UUO-kidney from TLR4 null mice than that from TLR4 wild-type mice. These results suggest that HA increases lymphangiogenesis in renal fibrosis model and also stimulates vascular endothelial cell growth factor-C production from macrophages through Toll-like receptor 4-dependent signal pathway.

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Machnik et al showed that the mononuclear phagocyte system is linked to the control of interstitial volume and blood pressure homeostasis. High salt diet activates the tonicity-responsive enhancer binding protein (TonEBP) in mononuclear phagocyte cells that are present in the skin. Activation of TonEBP increases VEGF-C production and increases lymphangiogenesis. Therefore, VEGF-C can be linked to maintain a normal blood pressure by regulating interstitial sodium accumulation state. Thus, I investigated the changes of serum and urine VEGF-C levels in patients with chronic kidney disease stage 3-4 and to evaluate the relationship between blood pressure and serum VEGF-C levels in the patients with CKD stage 5 and hemodialysis. I found that circulating levels of VEGF-C were decreased in patients with CKD, and the decrease of VEGF-C in patients with stage 3-4 CKD coincided with an increase in the urinary excretion of VEGF-C.
In conclusion, lymphangiogenesis may be a new avenue to ameliorate renal fibrosis and hypertension.