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Hypertension, Vascular Rarefaction and Angiopoietin-1

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Hypertension is a very common but incompletely understood disease, especially in its pathogenesis and vascular complications occurring in the cardiovascular research filed. There are many explanations for pathological mechanisms in hypertension, including adrenergic over-reactivity, renin-angiotensin-aldosteron system abnormality and constitutional-genetic-environmental factors.

Recently emerging evidences support a novel view of hypertension, as a disease of inadequate or abnormal responses to angiogenic factors and its related vascular rarefaction and remodeling.[1] To date, the best way to prevent or reduce hypertension-related vascular complications is lowering the blood pressure (BP).

However, recent studies have shown that controlling BP does not completely prevent cardiovascular or renal complication in hypertension, indicating that hypertension is one of the risk factors in developing cardiovascular complications or target organ damages (TODs).[2]

Therefore, we need more understanding about the vascular changes related not just to BP and its control, but also to endothelial dysfunction or vascular remodeling ragarding the angiogenic factors in the pathological mechanism and TOD process in hypertension.[2]

The series of articles of Kim et al. showed us the various favorable vascular effects of angiopoietin-1 (Ang-1), as an angiogenic factor, on vascular rarefaction and target organ damage in hypertension.[3][4]

Vascular Rarefaction in Hypertension Development and Target Organ Damage

The connection between microscopic vascular changes and angiogenesis is very important in the development and aggravation of hypertension. Underlying TOD resulting from hypertension is the functional and structural change in vasculature, especially in micro-vessels, which become constricted, under-perfused, and disappear, during the so-called rarefaction. Since the majority of the total vascular resistance occurs in small caliber vessels, i.e., less than 150 μm in diameter, vascular rarefaction could contribute to increased vascular resistance, TOD, and finally, vascular complications.[5] These damages and the disappearance of micro-vessels in hypertension are closely related to endothelial cell (EC) apoptosis originated from a variety of vascular stress.[6] Although rarefaction could be a consequence of hypertension, there is some evidence supporting a primary role for rarefaction in the process of hypertension. For example, early skin capillary rarefaction has been shown in normotensive offsprings of hypertensive ancestors.[7] Therefore, there is theoretical room for the therapeutic potential of angiogenic factors, especially Ang-1, to enhance angiogenesis and microvascular reconstitution to reduce both BP and target organ damage in hypertension.

Angiopoietin-1 and Its Actions on Vasculature

The proteins in the angiopoietin (Ang) family, i.e., Ang-1, 2, 3, and 4 are secreted protein ligands of tyrosinekinase with immunoglobulin and epidermal growth factor homolo-

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gy domain 2 (Tie2), and are mainly expressed in the endothelial hematopoietic stem cells and a subset of monocytes and macrophages.[8] Ang structure is composed of a carboxy-terminal fibrinogen-like domain, which is mainstay to bind, a central coiled-coil domain that oligomerizes the fibrinogen-like domains, and a short amino-terminal domain that superclusters these oligomers into variably-sized multimers.[8] Ang-1 is involved in angiogenesis and induces vascular stabilization by enhancing endothelial integrity; the non-leaky and tight vascular network formation is the particular characteristic of Ang-1, compared to vascular endothelial growth factor (VEGF).[8] Ang and Tie families have primary roles in the late stages of vascular development and adult vasculature, where they control remodeling and stabilization of the vessels. Thus, Ang-1 is required for correct organization and maturation of newly formed vessels, and promotes the quiescence and structural integrity of adult vasculature. Recently, Ang-1 has been shown to have potent effects on adult vessels, including survival promotion, vascular leakage inhibition, and inflammatory gene suppression.[9] Very diverse cellular or *in vivo* effects of Ang-1 have been clarified. Firstly, Ang-1 inhibits EC apoptosis, and also protects human umbilical vein endothelial cells, aortic and microvascular ECs from apoptosis induced by serum deprivation, hyperosmolarity and tumor necrosis factor-α.[9] Ang-1 reduces apoptosis in non-EC, e.g., mouse cortical neurons and skeletal and cardiac myocytes. This anti-apoptosis effect of Ang-1 occurs by activation of PI3K/Akt pathway, which is activated in response to Ang-1 through recruitment of the regulatory p85 subunit of PI3K to phosphorylated tyrosine residue 1,102 in the intraceullular domain of Tie2.[9] *In vivo*, Ang-1 increased vessel survival in studies of radiation-exposed mice, and decreased plasma leakage from skin vessels after treatment with inflammatory stimuli or VEGF.[10] In addition, Ang-1 has important roles in stimulating vascular remodeling, lymphatic proliferation and sprouting, and inhibition of leukocyte adhesion, allograft fibrosis, and endotoxemia.[9] Ang-2 shows very distinct features on angiogenesis, according to tissue environment; thus, Ang-1 stimulates Tie2 and Ang-2 can antagonize the effect of Ang-1 on Tie2. However, Ang-2 shows angiogenic activity only in the presence of VEGF.[8]

Angiopoietin-1, Endothelial Nitric Oxide Synthase Activation and Endothelial Cell Survival Enhancement in Hypertension

Previously, Kim et al. showed that treatment with one genetic variant of Ang-1, i.e., the Cartilage Oligomeric Matrix Protein-Ang-1 (COMP-Ang-1) plasmid, effectively reduced BP and significantly limited microvascular rarefaction and tissue damages in the heart and kidney of the spontaneously hypertensive rat (SHR) model.[3] These effects were completely abolished by pre-treatment with adenovirus carrying soluble Tie2 receptor, one day before COMP-Ang-1 gene transfer. The soluble Tie2 receptor competed with the native Tie2 on biding EC with its ligand, and inhibited ligand-induced Tie2 activation. Tie2 strongly phosphorylated by COMP-Ang-1 overexpression induced significant endothelial nitric oxide synthase (eNOS) production, as a downstream molecule of Tie2, and expressed higher amount of NO, compared to LacZ-treated SHR. Higher level of NO was confirmed by elevated serum level of nitrite, the metabolite of NO. The authors suggested that eNOS overexpression and elevated level of NO by COMP-Ang-1 induced reduction of BP, improvement of endothelial dysfunction, enhancement of EC survival and limitation of vascular rarefaction in the heart and kidney of SHR.

The new study of Kim et al. suggested a new potential mechanism of COMP-Ang-1 which is not depend on the NO to limit vascular rarefaction and reduce BP in SHR.[4] In that study, the authors pretreated SHR with a NOS inhibitor, i.e., N^W-nitro-L-arginine methyl ester (L-NAME) to exclude NO-mediated effects in COMP-Ang-1 gene delivery. Even after pretreatment with L-NAME, COMP-Ang-1 plasmid delivery using electrophoretic transfer effectively blocked the development of hypertension and attenuated microvascular rarefaction and arteriolar remodeling in the heart and kidney of SHR, compared to LacZ plasmid delivery control. The number of capillaries in the heart and kidney, counted by endothelial specific CD31 or RecA antibody staining, was significantly higher in the COMP-Ang-1 group in NOS-inhibited SHR, compared to LacZ-transferred SHR control. Myocardial fibrosis, glomerular fibrinoid necrosis and tubular interstitial fibrosis were also less observed in the COMP-Ang-1 group in NOS-inhibited SHR. What is the main molecular mechanism to reduce BP and limit vascular rarefaction of COMP-Ang-1 in L-NAME pretreated SHR? Although there are no confirmatory experiments in the study of Kim et al. we can suggest the anti-fibrotic and anti-inflammatory effects of Ang-1 as possible explanations. Similarly, the PI3 kinase/Akt pathway activation by COMP-Ang-1 to limit EC apoptosis and to enhance cellular survival can be a molecular mechanism to reduce rarefaction, vascular structural abnormality and BP elevation in L-NAME pretreated SHR. Further studies will be necessary to determine the molecular pathways of Ang-1 to limit vascular complications in NOS-inhibited SHR. This will give us important information to apply Ang-1 at clinical level, as a potential antihypertensive drug.

Potential Clinical Applications of Ang1

The *in vivo* effects of Ang-1 suggest that manipulation of this ligand may have therapeutic potential in some clinical ap-

plications, Because Ang-1 delivery shows rapid revascularization, EC apoptosis reduction, tight and non-leaky vascular network formation and blood pressure reduction, Ang-1 has potential indication in diabetic retinopathy, allograft vasculopathy, sepsis/endotoxemia and stroke.[9] Blocking the antibody for Ang-1 can also be used in malignancy.[9] Concurrently, up to 20 early phase clinical trials related to Ang are either ongoing or terminated, and most studies are focused on advanced solid tumor (from clinicaltrials.org). Is there any possibility to use Ang-1 as a potential anti-hypertensive drug in the future? More detailed and fine *in vitro* experiments and preclinical models to determine the molecular pathways to adjust blood pressure, vascular complications, and potential adverse reactions of Ang-1 should be performed in the near future, providing confirmation of Ang-1 effects in vascular rarefaction and hypertension.

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