ET-1 from endothelial cells is required for complete Angiotensin-II induced development of cardiac fibrosis and hypertrophy in mice

Nicolas Vignon-Zellweger[1], Suko Adiarto[2], Susi Heiden[1], Kazuhiko Nakayama[1], Keiko Yagi[1], Masashi Yanagisawa[3], Noriaki Emoto[1,2]. [1]Kobe Pharmaceutical University, Clinical Pharmacy, Japan, [2]Kobe University Graduate School of Medicine, Division of Cardiovascular Medicine, Department of Internal Medicine, Japan, [3]University of Texas Southwestern Medical Center, Howard Hughes Medical Institute.

Hypertensive patients develop cardiac hypertrophy and fibrosis with increased stiffness, contractile deficit and altered perfusion. Angiotensin II (Ang II) is an important factor in the promotion of this pathology. The effects of Ang II are partly mediated by endothelin-1 (ET-1) and transforming growth factor-β (TGFβ) via distinct intracellular pathways. The exact feature of these pathways and the intercellular communications involved remain unclear.

In this study, we explored the role of endothelial cell ET-1 in the development of Ang II induced cardiac fibrosis and hypertrophy.

For this purpose, we used mice with vascular endothelial cell specific ET-1 deficiency (VeETKO) and their wild type littermates (WT). Mice were infused for one week with Ang II (3.2mg/kg/day, n=12) or vehicle (0.15mol/L NaCl and 1mmol/L acetic acid, n=5), using subcutaneous mini-pumps. In the left ventricle of VeETKO mice, mRNA expression of ET-1 measured by real time-PCR was half as compared to WT littermates. This value increased in both genotypes after Ang II infusion and remained higher in WT mice. Systolic blood pressure measured by tail cuff increased similarly in both genotypes after infusion. Ang II-induced cardiac hypertrophy, interstitial and perivascular fibrosis were less pronounced in VeETKO mice compared to WT. In the left ventricle, Northern Blot analysis revealed that the increase of expression of connective tissue growth factor, TGF-β, collagen I and III in response to Ang II required endothelial ET-1. As shown by Western Blot, ET-1 was also necessary to the elevation in protein kinase C δ (PKCδ) abundance and ERK1/2 activation. Ang II induced elevation in PKCε abundance was however ET-1 independent.

Taken together, the paracrine effect of ET-1 from endothelial cell origin on cardiomyocytes and fibroblasts may be required for the complete Ang II induced development of cardiac fibrosis and hypertrophy. In our setting, the signaling pathway activated by ET-1 seems to involve rather PKCδ than PKCε.

This study supports a therapeutic potential of ET-1 blockade for the treatment of fibrotic heart disease.