[gw22-e0600]

## LOSS OF ACE2 AUGMENTS ANGIOTENSIN II-INDUCED MYOCARDIAL HYPERTROPHY AND REMODELING WITH INCREASED PROFILIN-1 EXPRESSION

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10.1136/heartjnl-2011-300867.90

**Introduction** Angiotensin (Ang) II, the main effector of the renin-angiotensin system (RAS), has recently shown to enhance the expression of Profilin-1, which functions as a crucial regulator in actin polymerisation and cytoskeleton remodelling by activation of the hypertrophic signalling cascades such as mitogen-activated protein kinase (MAPK) signalling, contributing to myocardial hypertrophy and ventricular remodelling. The key peptidase action of angiotensin-converting enzyme 2 (ACE2) is degradation of Ang II to Ang (1–7), functioning effectively as a negative regulator of the RAS. We hypothesised that loss of ACE2 accelerates myocardial hypertrophy and ventricular dysfunction by suppressing Ang II-mediated activation of MAPK signalling and Profilin-1 expression in heart.

**Methods & Results** Ten-week old male ACE2 knockout (ACE2KO, $Ace2^{-/y}$) and their littermate wildtype (WT, $Ace2^{+/y}$) mice were used. An osmotic minipump (model 1002; USA) was implanted subcutaneously at the dorsum of the neck to infuse a pressor dose of Ang II (1.5 mg/kg/day) or saline (Vehicle) for 14 days. We characterised the functional, structural and molecular changes in the heart in response to pressure overload by echocardiography, TaqMan real-time PCR, and Western blot analysis. Compared with WT mice, loss of ACE2 resulted in worsening myocardial hypertrophy and pathological remodelling in ACE2 KO mice in response to Ang II, associated with increased expression of Profilin-1 and enhanced levels of hypertrophy markers (atrial natriuretic factor and brain natriuretic peptide). These changes were linked with greater activation of protein kinase Ca (PKCa) protein and phosphorylation of the extracellular signal-regulated protein kinase (ERK1/2), Janus kinase 2 (JAK2)/signal transducer and activator of transcription 3 (STAT3), but not p38-mitogen-activated protein kinase (MAPK) signalling in Ang II-infused ACE2 KO mice.

**Conclusions** Loss of ACE2 augments Ang II-induced myocardial hypertrophy and adverse remodelling by the enhanced Profilin-1 expression. These changes have been associated with activation of PKC signalling, the MAPK and JAK2/STAT3 phosphorylation pathways, suggesting a critical role of ACE2 in the suppression of Ang II-mediated myocardial hypertrophy, ventricular remodelling and heart failure. Drugs that influence the

expression and activity of ACE2 may be potential avenues in the prevention and treatment of heart diseases. This work was supported by National Natural Science Foundation of China (Grant 30973522 & 30700328), and the Canadian Institute for Health Research (GYO, 86602 & 84279).