Objectives INTRODUCTION: Angiotensin (Ang) II is known to activate matrix metalloproteinases (MMPs), leading to degradation of extracellular matrix (ECM) proteins and myocardial remodelling. Angiotensin-converting enzyme-2 (ACE2) is a carboxypeptidase that metabolises Ang II to yield Ang-(1–7), essentially negatively regulating the renin-angiotensin system. We hypothesised that loss of ACE2 exacerbates myocardial remodelling by modulating the levels of MMPs.

Methods 10-week old male wildtype (WT, $Ace2^{+/y}$) and ACE2 knockout (ACE2KO, $Ace2^{-/y}$) mice received with mini-osmotic pumps (model 1002; USA) with a pressor dose of Ang II (1.5 mg kg^{-1} d^{-1}) or saline for 2 weeks. Pro and cleaved forms of MMP2 and MMP9 were detected by gelatine zymography, and total collagenase and gelatinase activities were measured using fluorescent-based activity assays from EnzCheck (Molecular Probes). The membrane-anchored collagenase membrane type 1 (MT1)-MMP, the fibrotic factors transforming growth factor-β1 (TGF-β1) and fibronectin levels in heart were determined by TaqMan real-time PCR and western blotting analyses, respectively.

Results In response to chronic stimulation by Ang II, there were significant increases in myocardial expression of MMP2, MMP9 and MT1-MMP in both WT and ACE2KO mice with elevated plasma Ang II levels. Furthermore, loss of ACE2 resulted in greater increases in Ang II-mediated expression of pro MMP2 and active MMP2 and MMP9 in ACE2KO hearts associated with enhanced expression of MT1-MMP, TGF-β1 and fibronectin and elevated activities of gelatinase and collagenase. These changes were linked with a degraded and disorganised ECM in the Ang II-treated ACE2KO heart by picrosirius red staining.

Conclusions ACE2 deficiency exacerbates Ang II-mediated adverse myocardial remodelling by modulating the levels of MMP2, MMP9 and MT1-MMP and enhancing the expression of TGF-β1 and fibronectin, implying a critical role of ACE2 in regulating the balance between generation and degradation of myocardial extracellular matrix and potential therapeutic approaches by enhancing ACE2 action for patients with heart diseases. This work was supported by National Natural Science Foundation of China (30973522 & 81170246), Shanghai Pujiang Talents Programme (11PJ1408300) and the Canadian Institute for Health Research (86602 & 84279).

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ANGIOTENSIN II-MEDIATED MYOCARDIAL EXPRESSION OF MMP2, MMP9 AND MT1-MMP WERE ENHANCED IN ACE2-NULL MICE

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