CARDIAC-SPECIFIC KNOCKOUT OF CAPN4 ATTENUATES MYOCARDIAL REMODELLING AND IMPROVES FUNCTION AFTER MYOCARDIAL INFARCTION IN MICE

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1Jian Ma, 2Tianqing Peng. 1Department of Cardiology, Shanghai 6th People’s Hospital, Shanghai JiaoTong University School of Medicine, Shanghai 200233, China; 2Critical Illness Research, Lawson Health Research Institute, London, Ontario, Canada N6A 4G5

Objectives Calpain has been implicated in myocardial injury after myocardial infarction (MI). However, no direct evidence is available on the role of calpain in post-MI myocardial remodelling and dysfunction. The present study investigated the effects of cardiomyocyte-specific knockout of Capn4, essential for calpain-1 and calpain-2 activities on myocardial remodelling and function following MI.

Methods A novel mouse model with cardiomyocyte-specific deletion of Capn4 (Capn4-ko) was generated; MI was induced by left coronary artery ligation; Left ventricular pressure–volume loop and Echocardiography were used to assess changes in left ventricle geometry and function; Sirius red staining was used for analysis of myocardial collagen deposition; Paraffin sections were stained for membranes with FITC-conjugated wheat germ agglutinin (WGA) and for nuclei with DAPI For cardiomyocyte cross-sectional area; Apoptosis was assessed by caspase-3 activity measurement and TUNEL staining; MMP-2 and MMP-9 activities in heart tissue lysates were assessed by using MMP-2 and MMP-9 Assay Kits, respectively.

Results Deficiency of Capn4 significantly reduced the protein levels and activities of calpain-1 and calpain-2 in the Capn4-ko heart. In vivo cardiac function was significantly improved in Capn4-ko mice at 7 and 30 days after MI compared with their wild-type littermates. Deletion of Capn4 reduced adverse remodelling after MI as evidenced by limitation of infarct expansion and infarct zone thinning, and prevention of left ventricle dilation of Capn4-ko mice. Furthermore, myocardial collagen deposition and cardiomyocyte cross-sectional areas were significantly attenuated in Capn4-ko mice, which were accompanied by down-regulation of pro-fibrotic genes and hypertrophic genes. These effects of Capn4 knockout correlated with a decrease in cardiac apoptosis in the peri-infarct area, down-regulation of inflammatory mediators and normalisation of matrix metalloproteinase (MMP)-9 activity in the non-infarct areas of Capn4-ko mice after MI.

Conclusions Cardiomyocyte-specific knockout of calpain attenuates myocardial adverse remodelling and improves myocardial function after MI. These beneficial effects of calpain disruption may result from inhibition of cardiac apoptosis, inflammation and MMP-9 activity.