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

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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.