p66ShcA adaptor protein facilitates heart rupture via activation of MMP-2 in an in vivo model of myocardial infarction in mice.

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Purpose: Heart failure is a growing problem worldwide. Cardiac remodeling, which features aseptic inflammation, metalloproteinase (MMP) activation and induction of matricellular proteins, contributes to heart failure progression after myocardial infarction (MI). The ShcA gene encodes three isoforms: p46-, p52- and p66ShcA, which are crucial for embryonic development of the heart. The p66ShcA isoform regulates mitochondrial respiration and oxidative stress. p66ShcA deletion protects against acute myocardial ischemia ex vivo. We studied the role of p66ShcA in chronic cardiac ischemia and cardiac remodeling in vivo. We aimed to find whether (a) p66ShcA expression was induced by MI, (b) p66ShcA was involved in cardiac remodeling and (c) to elucidate underlying mechanisms with focus on MMP and inflammation.

Materials and Methods: MI was induced in vivo via occlusion of the left descending coronary artery in C57Bl/6 male mice. Cardiac expression of p66ShcA in wild type mice (WT) was evaluated serially postinfarction (n=105). The functional effects of p66ShcA were evaluated in knockout mice (p66KO) compared to WT (n=72). Hearts from WT and p66KO were harvested three days postinfarction to evaluate infarct size, expression of MMP and matricellular proteins. Simultaneously, spleens were collected for splenocytes isolation (n=5 in each group). Interleukins expression in the splenocytes was assessed by flow cytometry. Six weeks after MI, survival, heart function and cardiac fibrosis were evaluated (n=19 per group). Mouse embryonic fibroblasts with p66ShcA knockdown were used to study MMP-2 expression.

Results: p66ShcA expression increased transiently during the first weeks postinfarction. p66KO mice had increased survival after MI (p=0.005) and reduced occurrence of heart rupture (p=0.04). Three days postinfarction, cardiac MMP-2 and matricellular proteins, such as connective tissue growth factor and thrombospondin-1, were down-regulated in the hearts of p66KO compared to WT mice. After MI, p66KO splenocytes had a lower expression of IL-17 and IL-4 than WT mice. Six weeks after MI, p66KO mice had attenuated both fibrosis and left ventricular dilatation. At the same time, p66ShcA depletion in vitro attenuated activation of MMP-2.

Conclusions: The p66ShcA isoform is involved in adverse cardiac remodeling after myocardial infarction. Deletion of p66ShcA prevented cardiac rupture and improved survival. The underlying mechanism was partly elucidated: p66ShcA activates MMP-2 and regulates expression of IL-4 and IL-17. The p66ShcA can be a potential target for preventing adverse cardiac remodeling postinfarction.