

## CCN2/CTGF prevents heart failure and improves survival after myocardial infarction

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**Background:** Myocardial CCN2/CTGF is robustly induced in heart failure (HF). Yet, its role in the pathophysiologic mechanisms of HF remains unresolved.

**Methods and results:** To elucidate the role of myocardial CTGF in HF, transgenic mice with cardiac-restricted overexpression of CTGF (Tg-CTGF) were employed and compared with non-transgenic controls (NLC). Myocardial infarction was induced by ligation of the LAD in Tg-CTGF (n=22) and NLC mice (n=21). Sham-operated animals underwent the same procedure without ligation of the artery. Area at risk was estimated in a separate group of animals sacrificed immediately after ligation of the left coronary artery and perfusion with Evans blue dye. Area at risk was similar among Tg-CTGF and NLC mice ( $42.7 \pm 1.6\%$ , n=8 vs  $40.4 \pm 2.1\%$ , n=8, p=0.39). During follow-up, significant increase of survival was found in Tg-CTGF mice (63.6% vs. 38.1%, p<0.05). In vivo pressure-volume analysis performed after 4 weeks displayed preserved cardiac performance in Tg-CTGF vs. NLC mice. End-point analysis revealed attenuation of cardiac hypertrophy in Tg-CTGF vs. NLC mice (Heart weight/body weight ratio;  $5.3 \pm 0.2\text{mg/g}$ , n=14 vs  $8.0 \pm 0.9\text{mg/g}$ , n=9, p<0.05). Selective upregulation of GRK5 in cardiac myocytes of Tg-CTGF hearts were found and confirmed as the mediator of  $\beta$ AR desensitization. Tg-CTGF hearts also displayed increased phosphorylation of AKT(Ser473) and GSK-3 $\beta$ (Ser9). Interestingly, induction of myocardial collagen contents four weeks after myocardial infarction, determined by quantitative HPLC of hydroxyproline, was lower in Tg-CTGF mice than in NLC-mice.

**Conclusion:** This study uncovers novel, unexpected cardioprotective properties of CTGF in ischemic HF. Myocardial CTGF prevents development of HF and improves survival after myocardial infarction, possibly due to activation of salvage kinase pathways and inhibited neuro-humoral stimulation of the heart.