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CCN2/CTGF attenuates myocardial hypertrophy and cardiac dysfunction upon chronic pressure-overload ☆

Jørgen Gravning [a,c], Mohammed Shakil Ahmed [a,c], Thomas G. von Lueder [a,c], Thor Edvardsen [a,b,c], Håvard Attramadal [a,b,c,*]

[a] Institute for Surgical Research, Oslo University Hospital, Rikshospitalet and University of Oslo, Norway
[b] Department of Cardiology, Oslo University Hospital, Rikshospitalet and University of Oslo, Norway
[c] Center for Heart Failure Research, University of Oslo, Norway

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ABSTRACT

Background: Myocardial CCN2/CTGF (connective tissue growth factor) is strongly induced in heart failure (HF) and acts as a cardioprotective factor in ischemia/reperfusion injury. However, its functional role in myocardial hypertrophy remains unresolved.

Methods and results: Transgenic mice with cardiac-restricted overexpression of CTGF (Tg-CTGF) and non-transgenic littermate control (NLC) mice were subjected to chronic pressure-overload by abdominal aortic banding. After 4 weeks of persistent pressure-overload, a time point at which compensatory hypertrophy of the left ventricle (LV) prevails, Tg-CTGF mice displayed diminished increase of LV mass compared with NLC. At study end-point after 12 weeks of sustained aortic constriction, the mice displayed LV dilatation and reduced cardiac function. Repeated transthoracic echocardiography during the 12 weeks of chronic pressure-overload, revealed attenuation of LV dilatation and virtually sustained systolic function in Tg-CTGF mice compared with NLC mice. Also, increase of LV mass was blunted in Tg-CTGF versus NLC mice at study end-point. Consistently, increases of myocardial ANP, BNP and skeletal α-actin mRNA levels were blunted in Tg-CTGF mice subjected to chronic pressure-overload. Furthermore, cardiac myocytes from Tg-CTGF mice displayed increased phospho-NFATc2 levels and attenuated hypertrophic response upon stimulation with α_1-adrenoceptor agonist, indicating that CTGF attenuates hypertrophic signaling in cardiac myocytes. Increase of myocardial collagen contents in mice subjected to aortic banding was similar in Tg-CTGF and NLC mice, indicating that CTGF have minimal impact on myocardial collagen deposition.

Conclusion: This study provides novel evidence that CTGF attenuates cardiac hypertrophy upon chronic pressure-overload due to inhibition of signaling mechanisms that promote pathologic myocardial hypertrophy.

1. Introduction

Chronic increase of cardiac workload, for example such evoked by hypertension or myocardial infarction, elicits compensatory cellular responses that help the heart adjust to the increased workload. These cellular responses include, but are not restricted to, cardiac myocyte hypertrophy. The myocardial gene expression pattern associated with chronic increase of cardiac workload reflects conversion to a fetal cardiac phenotype. This fetal gene expression pattern also includes induction of several autocrine/paracrine factors whose role in the postnatal cardiac physiology or pathophysiology is poorly understood.

One of the genes that are substantially increased in heart failure of various etiologies is CCN2/CTGF — connective tissue growth factor. CTGF is a 38 kDa matricellular protein and member of the CCN gene family (acronym of Cyr61, CTGF/Fisp-12, Nov) [1–3]. These proteins are secreted, heparin-binding, and extracellular matrix (ECM)-associated proteins involved in multiple cellular events including ECM production, cell adhesion, cell proliferation, or in some cell types, apoptosis [4,5].

In a previous study from our laboratory, enhanced resistance towards ischemia/reperfusion injury was observed both in transgenic mice with cardiac-restricted overexpression of CTGF (Tg-CTGF) and in Langendorff-perfused hearts pre-treated with recombinant human CTGF (rh-CTGF) before ischemia, due to increased activity of the Akt/GSK-3β signaling pathway [6]. The same study demonstrated that cardiac-restricted expression of CTGF resulted in minimal increase of myocardial fibrosis per se. In a recent study of myocardial infarction and ischemic heart failure in Tg-CTGF mice and corresponding control mice, we also report that CTGF causes

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* Corresponding author at: Institute for Surgical Research, Oslo University Hospital, Rikshospitalet, P.O. Box 4950, Nydalen, NO-0424 Oslo, Norway. Tel.: +47 23073520; fax: +47 23073530.
E-mail address: havard.attramadal@medisin.uio.no (H. Attramadal).

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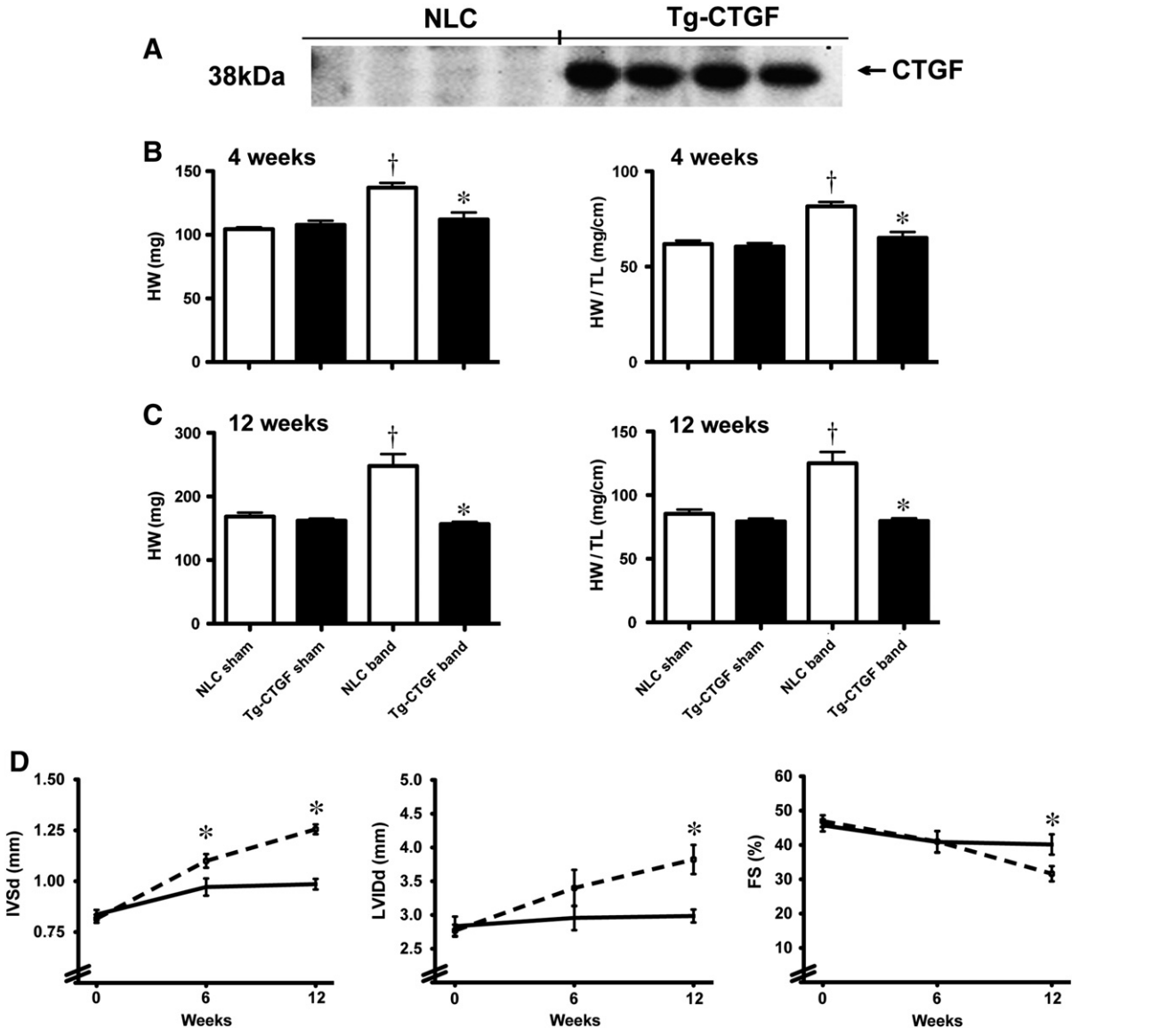

Fig. 1. Compensatory myocardial hypertrophy and cardiac remodeling following aortic banding-induced chronic pressure-overload. (A) Immunoblot demonstrating myocardial contents of CTGF (immunoreactive CTGF migrating at 38 kDa) in Tg-CTGF mice vs. NLC mice. (B) Histograms of cardiac mass (HW; heart weight) and cardiac mass related to tibia length (HW/TL) of Tg-CTGF (n = 5) and NLC mice (n = 5) after 4 weeks of chronic pressure overload. (C) Histograms of cardiac mass (HW; heart weight) and cardiac mass related to tibia length (HW/TL) of Tg-CTGF (n = 9) and NLC mice (n = 9) after 12 weeks of chronic pressure overload compared with respective sham-operated mice. (D) Time course of end-diastolic interventricular septum thickness (IVSd), internal left ventricular diameter (LVIDd) and fractional shortening (FS) following abdominal aortic banding determined by successive trans-thoracic echocardiography Tg-CTGF mice (—■—; n = 7) and NLC mice (--□--; n = 9) from baseline (day −1) to 12 weeks after induction of pressure-overload. All data are mean ± SEM. †$P<0.05$ vs. NLC sham; *$P<0.05$ vs. NLC band.

enhanced healing of the infarction and attenuation of left ventricular remodeling [7]. However, since the attenuated remodeling of the left ventricle may also be due to enhanced infarct healing, the left coronary artery ligation model may not be suitable to assess the direct effect of CTGF on myocardial remodeling in heart failure. On the other hand, data from investigations of another transgenic mouse-model with cardiac-restricted overexpression of CCN2/CTGF have reported somewhat enhanced fibrosis upon pressure-overload [8]. The study, which did not include assessments of cardiac function, reported similar increase of cardiac hypertrophy in the CTGF-transgenic mice and non-transgenic control mice subjected to aortic banding [8]. The subtle and somewhat inconclusive findings of the latter report could be due to the rather modest overexpression of CTGF in the heart (4-fold overexpression). Thus, it could be argued that such a low overexpressing model may not provide the pharmacologic levels of CTGF needed to reveal all of its functions. In this respect, yet another study of cardiac-restricted overexpression of CTGF reported preserved cardiac function following chronic infusion of angiotensin II [9]. Thus, we therefore hypothesized that CTGF also might also confer beneficial responses also upon non-ischemic chronic pressure overload.

In order to dissect these diverging findings and elucidate the actions of CTGF in the heart, a transgenic high-overexpressor would be required. Thus, we investigated the functional effects of both short-term and long-term chronic pressure-overload in the Tg-CTGF mice generated in our laboratory, which display 70-fold overexpression of myocardial CTGF levels. The myocardial gene expression signature of the Tg-CTGF mice provided cues of CTGF-induced activation of anti-hypertrophic gene programs [6]. The current study unravels the novel findings of CTGF as a protective factor with anti-hypertrophic