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Krüppel-like transcription factor 11 (KLF11) overexpression inhibits cardiac hypertrophy and fibrosis in mice

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ABSTRACT

The Krüppel-like factors (KLFs) belong to a subclass of Cys2/His2 zinc-finger DNA-binding proteins. The KLF family member KLF11 is originally identified as a transforming growth factor β (TGF-β)-inducible gene and is one of the most studied in this family. KLF11 is expressed ubiquitously and participates in diabetes and regulates hepatic lipid metabolism. However, the role of KLF11 in cardiovascular system is largely unknown. Here in this study, we reported that KLF11 expression is down-regulated in failing human hearts and hypertrophic murine hearts. To evaluate the roles of KLF11 in cardiac hypertrophy, we generated cardiac-specific KLF11 transgenic mice. KLF11 transgenic mice do not show any difference from their littermates at baseline. However, cardiac-specific KLF11 overexpression protects mice from TAC-induced cardiac hypertrophy, with reduced radios of heart weight (HW)/body weight (BW), lung weight/BW and HW/tibia length, decreased left ventricular wall thickness and increased fractional shortening. We also observe lower expression of hypertrophic fetal genes in TAC-challenged KLF11 transgenic mice compared with WT mice. In addition, KLF11 reduces cardiac fibrosis in mice underwent hypertrophy. The expression of fibrosis markers are also down-regulated when KLF11 is overexpressed in TAC-challenged mice. Taken together, our findings identify a novel anti-hypertrophic and anti-fibrotic role of KLF11, and KLF11 activator may serve as candidate drug for heart failure patients.

1. Introduction

Cardiac hypertrophy is a common response of cardiomyocytes to a variety of physiologic and pathologic stimuli. In mammalian, cardiomyocytes lose their ability to divide soon after birth. The only way for mammalian cardiomyocytes to deal with sustained increase in workload requirement is to undergo hypertrophy. During hypertrophy, cardiomyocytes not only grow in size but also add sarcomeres and induce the expression of a group of genes, which are predominantly expressed during fetal heart development. Hypertrophic growth is initially a compensatory response that helps maintain cardiac function by reducing wall stress, but it eventually leads to the development of heart failure and sudden death due to arrhythmias [1,2]. Presently, heart failure has been one of the leading causes of morbidity and mortality worldwide.

Hypertrophy of cardiomyocytes is considered to result from imbalance between pro-hypertrophic and anti-hypertrophic factors and their downstream mechanisms controlling cell growth. In recent years, much progress has been made in our understanding of hypertrophic activators [3]. However, relatively little is known about endogenous negative regulators of cardiac growth, which may have potential to block the cardiac hypertrophic responses [2]. Although some transcription factors, in addition to nuclear factor of activated T cells (NFAT), GATAs, nuclear factor kappa B (NF-κB), myocyte enhancer factor-2 (MEF2), and Nkx2.5, have been identified to participate in cardiac hypertrophic [1,4,5], it's still unknown whether other transcription factors may act in hypertrophy and heart failure. In addition, most of those factors promote the development of cardiac hypertrophy. The negative transcription factors in cardiac hypertrophy is still largely unknown.

Krüppel-like factors (KLFs), Sp1-like zinc finger transcription factors, are highly conserved in organisms ranging from flies to human and are characterized by the presence of a DNA-binding domain with three highly conserved zinc finger motifs as well as a variant carboxyl-terminal end [6]. The transcription factor KLF11 (also called TIEG2), which inhibits cell growth, is a member of the KLF family. Relatively, KLF11 is the best-studied member of KLF family. KLF11 controls cell growth by sensing TGF-β [7]. In addition, KLF11 considerably participates in type II diabetes and regulates hepatic lipid metabolism [8,9]. However, the role of KLF11 in cardiovascular system is unknown.

Here in the present study, we identify KLF11 as a negative transcription factor in the development of cardiac hypertrophy. We found that KLF11 expression is down-regulated in failure human

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hearts and hypertrophic murine hearts. By using KLF11 transgenic mice, we demonstrated that KLF11 overexpression inhibited TAC-induced cardiac hypertrophy and fibrosis.

2. Materials and methods

2.1. Animals

Transgenic mice with cardiac-restricted expression of KLF11 were generated using a cDNA amplified from a plasmid encoding human KLF11 (ORIGEN, plasmid 8462), which was sub-cloned into the α-MHC promoter vector. Transgenic mice expressing KLF11 were generated in the FVB mouse strain according to the standard procedure of the Shanghai Jiaotong University Transgenic facility. At 2–3 weeks of age, tail DNA was analyzed to confirm mice positive for the transgene by genotyping with primers: Forward, 5′-TCTGACTCTGGGGATGTCAC-3′; Reverse, 5′-CGGCAATCTG-GAGTCTGGA-3′. After two injections, 3 (founders) out of 6 pups were tested to be positive. The transgenic mice were backcrossed to C57BL6 mice to obtain cardiac-specific KLF11 transgenic mice in the C57BL/6 background. All experiments studying cardiac hypertrophy were performed using male C57BL/6 mice. Non-transgenic littermates were used as controls.

2.2. Induction of hypertrophy in mice

ISO and Ang II were infused chronically by implanting osmotic minipumps (ALZET, model 2002) into the peritoneal cavity of mice as described in previous publication [10]. Pressure overload hypertrophy was induced by TAC of the ascending aorta of mice, as described elsewhere [11]. The measurement of cardiac hypertrophy, myocyte cross-sectional area, fibrosis and the expression of hypertrophic marker genes were carried out essentially as described [12].

2.3. Echocardiography of mice

Transthoracic echocardiography in mice was performed as described previously [10].

2.4. Human heart samples

Human heart samples were obtained from the Shanghai Chest Hospital Cardiac Transplant Program. Informed consent was obtained from all patients participating in this study. All procedures involving human tissue use were approved by the Shanghai Jiaotong University. Control samples were obtained intraoperatively from non-failing hearts undergoing ventricular corrective surgery or from donor dysfunctional hearts. Failing heart specimens were obtained from diseased hearts that were removed during orthotropic heart transplantation.

2.5. Quantitative real-time PCR (q-PCR)

q-PCR was used to detect the mRNA expression levels of hypertrophic and fibrotic markers. Total RNA was extracted from frozen, pulverized mouse cardiac tissue using TRIZol (Invitrogen) and cDNA was synthesized using 1 μg RNA with the Advantage RT-for-PCR kit (BD Biosciences). We quantified PCR amplifications using SYBR Green PCR Master Mix (TAKARA) and normalized results against GAPDH gene expression. The primers used are listed in Supplementary Table 1.

2.6. Western blotting

Cardiac tissues were lysed in RIPA lysis buffer with mixture of protease inhibitors. 40 μg cell proteins were applied to 12% SDS–polyacrylamide gel. After electrophoresis, the proteins were transferred to PVDF membranes, which were then blocked in 5% fat-free milk for 1 h. The membranes were probed with primary antibody for KLF11 (Abcam, ab61207), or GAPDH (Abcam, ab37168) at 4 °C overnight, and then the membranes were washed and incubated with HRP-conjugated secondary antibody (in 5% fat-free milk) for 1.5–2 h and finally visualized using Chemiluminescent ECL reagent (Beyotime).

2.7. Histological analysis

Hearts were excised, washed with saline solution, and placed in 10% formalin. Hearts were cut transversely close to the apex to visualize the left and right ventricles. Several sections of heart (4–5 μm thick) were prepared and stained with H&E for histopathology or picrosirius red for collagen deposition and then visualized by light microscopy. Fibrotic area was measured using a quantitative digital image analysis system (Image-Pro Plus 6.0). For myocytes cross-sectional area, sections were stained for membranes with WGA (Invitrogen). A single myocyte was measured with an image quantitative digital analysis system (NIH Image J, version 1.47).

2.8. Statistical analysis

All values are expressed as the mean ± SEM. Statistical differences among groups were determined using either Student's *t* test (for two groups) or one-way ANOVA (for more than two groups) using Graph-Pad Prism Software.

3. Results

3.1. KLF11 expression reduces in human failing heart and murine hypertrophic heart

To assess the potential participation of KLF11 in human heart failure, we tested the protein and mRNA levels of KLF11 in non-failing and failing heart samples. Our results showed that KLF11 protein and mRNA levels decreased in human failing heart significantly (Fig. 1A and B). Those results implicated that KLF11 might participate in human heart failure. Because we have only two non-failing and two failing heart samples, we next wanted to confirm the conclusion in mice with a larger animal number. Cardiac hypertrophy is a pathological base of heart failure, we tried to use this model to study the role of KLF11 in heart disease. To explore the changes in KLF11 expression in murine hypertrophic hearts, we induced cardiac hypertrophy in mice by TAC surgery or infusing mice with angiotensin II (Ang II) or ISO for 4 weeks. Then, total protein and RNA were extracted to analyze KLF11 expression level. As shown in Fig. 1C and D, the protein and mRNA levels of KLF11 were markedly down-regulated in hypertrophic mice in the three models of cardiac hypertrophy. Taken together, those findings demonstrated that KLF11 is down-regulated in failing or hypertrophic heart, and KLF11 may play certain roles in cardiac hypertrophy and subsequent heart failure.

3.2. Generation of KLF11 transgenic mice

As we have found the expression change and potential participation of KLF11 in cardiac hypertrophy, we next wanted to know whether KLF11 is critical for the development of cardiac

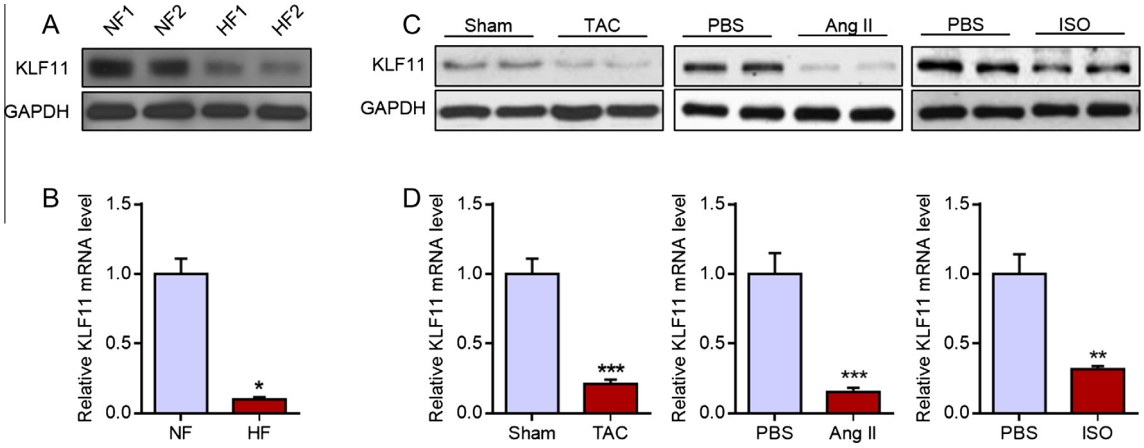

Fig. 1. KLF11 expression decreases in human failing hearts and mice hearts with hypertrophy. (A and B) KLF11 protein and mRNA levels decrease in human failing hearts. Non-failing (NF) or failing (HF) hearts from patients were obtained and protein and RNA were extracted and subjected to Western blot and q-PCR analysis respectively. GAPDH was used a loading control in the Western blot analysis. Two non-failing and two failing human heart samples are included in this study. $^{*}p < 0.05$ *vs.* NF. (C and D) KLF11 protein and mRNA levels decrease in mice hearts with hypertrophy. 8–12 weeks old male wide type C57LB6 mice were subjected to TAC surgery or chronic infusion with angiotensin II (Ang II) or ISO for 4 weeks. Mice hearts were extracted for protein and RNA, followed by Western blot or q-PCR analysis respectively. $n = 5$ in each group in Fig. 1D. $^{**}p < 0.01$ and $^{***}p < 0.0001$ *vs.* Sham or PBS treatment.

hypertrophy in mice. To this purpose, we generated cardiac-specific KLF11 transgenic mice (Fig. 2A). Three lines of transgenic mice were obtained and no significant difference appeared among the three lines of mice. Therefore, we chose line 2 randomly for further study. The expression pattern of KLF11 in different tissues was shown in Fig. 2C, which indicated that the enthetic expression of human KLF11 was restricted to the hearts. Although KLF11 were previously reported to participate in type II diabetes and hepatic lipid metabolism [8,9], we did not observe any difference in blood glucose, liver weight, and body weight between the transgenic mice and their non-transgenic littermates during our experiments (data not shown). At baseline, KLF11 transgenic mice had no noticeable cardiac abnormalities (Fig. 2D–F). In addition, no difference in hypertrophic fetal gene levels between WT and KLF11-transgenic mice was observed (Fig. 2G).

3.3. KLF11 overexpression represses TAC-induced cardiac hypertrophy

Although we did not observe any difference between KLF11-transgenic mice and non-transgenic littermates at baseline, we were still interested whether those mice response differently to hypertrophic stimuli. To evaluate the potential effect of KLF11 on hypertrophy *in vivo*, we induced cardiac hypertrophy in KLF11-Tg and mice and their non-transgenic wide type littermates by

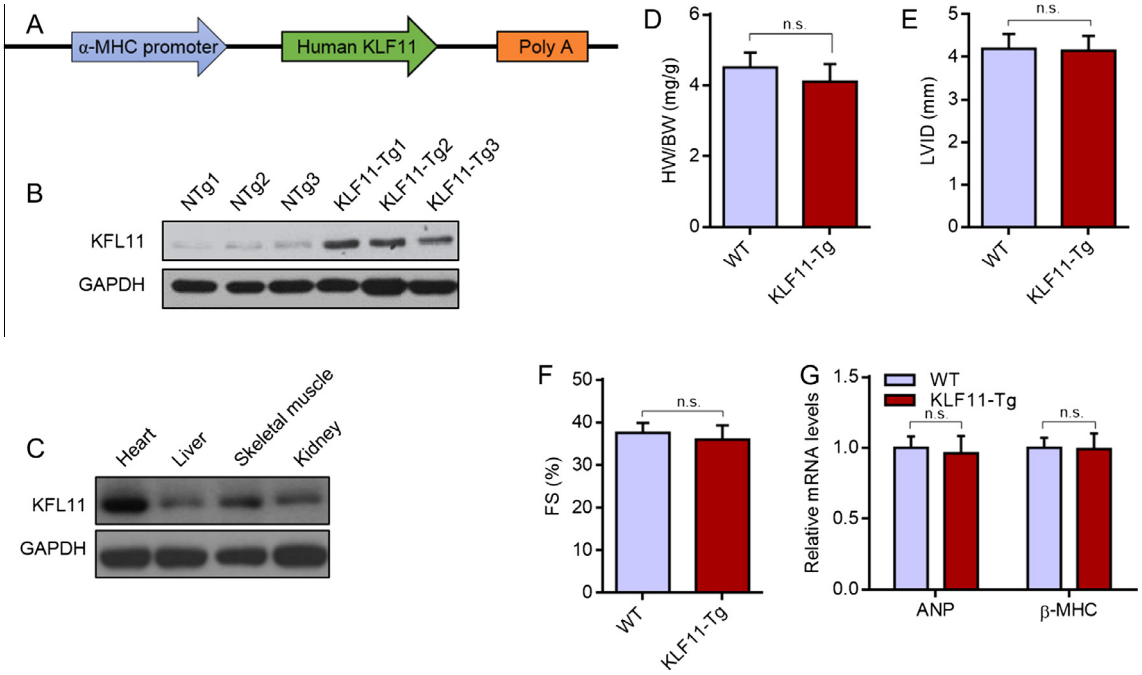

Fig. 2. Transgenic (Tg) mice generation. (A) A schematic of Tg construct used to generate human KLF11-Tg mouse lines. (B) KLF11 expression analysis in three non-transgenic (N-Tg) and three KLF11-Tg mouse lines. (C) Expression pattern of hKLF11 in heart, liver, skeletal muscle, kidney from KLF11-Tg mice. (D–F) KLF11-Tg mice do not show any difference in heart function compared to their non-transgenic littermates. HW, heart weigh; BW, body weight; LVID, left ventricular internal diameter; FS, fractional shortening; ANP, atrial natriuretic peptide; n.s., no significance. $n = 10$ in each group of Fig. 2D–F; $n = 5$ in each group of Fig. 2G.

surgically creating TAC. Non-transgenic mice subjected to TAC for 4 weeks developed massive cardiac hypertrophy, as indicated by an increased radios of heart weight (HW)/body weight(BW), lung weight (LW)/BW and HW/tibia length (TL, Fig. 3A–C), increased left ventricular wall thickness (Fig. 3D) and decreased fractional shortening (Supplementary Table 2). Those changes were accompanied by an increase in cardiomyocyte cross-sectional area (Fig. 2E–G). Interestingly, the hearts of KLF11-transgenic mice did not undergo similar pathological growth after being subjected to TAC (Fig. 3A–G). KLF11-transgenic were less sensitive to TAC treatment and had better cardiac function when hypertrophy occurred. During the development of cardiac hypertrophy, many fetal genes express again. Therefore, we further extracted the RNA from the hearts and tested the expression of hypertrophic fetal genes. In consistent with the pathological results, hypertrophic fetal genes were markedly down-regulated in KLF11-Tg mice compared to non-transgenic wide type mice after TAC treatment (Fig. 3H–J). Those data indicates that KLF11 overexpression is capable of abrogating the development of pathologic cardiac hypertrophy.

3.4. KLF11 overexpression reduces TAC-induced cardiac fibrosis

As hypertrophic heart is always accompanied with fibrosis, we then evaluated the cardiac fibrosis in hypertrophic hearts. Pronouncedly, KLF11 overexpression repressed TAC-induced perivascular and interstitial fibrosis, two markers indicating cardiac fibrosis (Fig. 4A). Quantitative analysis indicated that the fibrosis volume decreased to 39.8% in the left ventricle of KLF11 transgenic mice compared to wide type mice. In consistence with those findings, the expression of fibrosis markers were also markedly down-regulated in KLF11 transgenic mice underwent TAC compared with their non-transgenic littermates (Fig. 4C–G). Taken together, KLF11 inhibits TAC-induced cardiac fibrosis.

4. Discussion

Our work uncovered a physiological role of KLF11 in maintaining cardiac homeostasis, demonstrated the feasibility of targeting KLF11 to restore cardiac homeostasis in animals with cardiac hypertrophy. We showed that KLF11 was down-regulated in human failing hearts and murine hypertrophic hearts. Then we generated a cardiac-specific KLF11 transgenic mice line to study the role of KLF11 in cardiac hypertrophy induced by TAC. We found that KLF11 overexpression blunted the development of cardiac hypertrophy and fibrosis, and down-regulated the expression of hypertrophic fetal genes and genes involved in cardiac fibrosis.

Although there has been an explosion of studies on KLFs in a broad variety of tissues and disease states, the reports describing

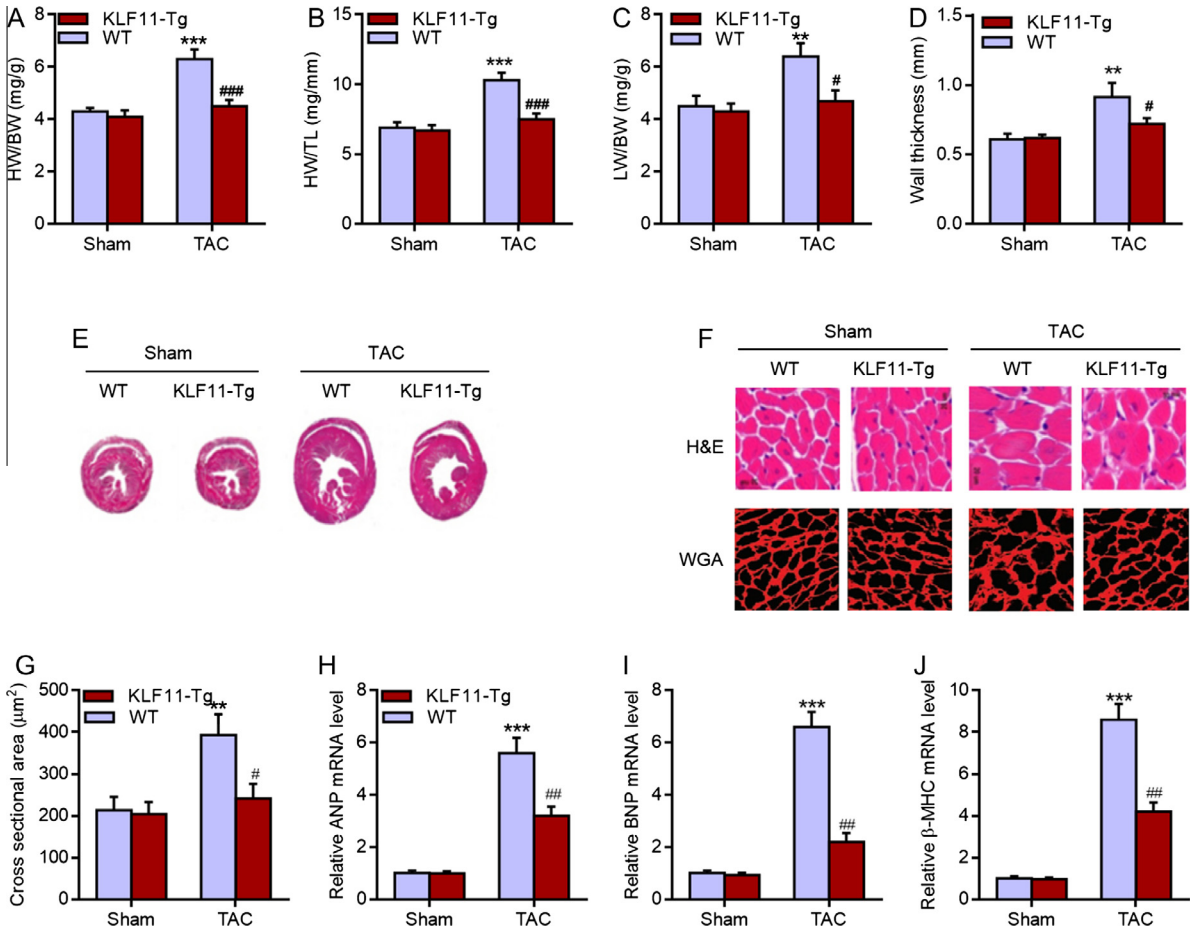

Fig. 3. KLF11 overexpression blocks TAC-induced cardiac hypertrophy. Wide type (WT) non-transgenic and KLF11-Tg mice of 8–12 weeks old were subjected to Sham or TAC surgery for 4 weeks and the heart samples were analyzed. (A–C) HW/BW, HW/tibia length (TL) and lung weight (LW)/BW ratios of WT and KLF11-Tg mice underwent control surgery (Sham) or TAC for 4 weeks. (D) Left ventricular wall thickness of WT and KLF11-Tg mice underwent Sham or TAC surgery. (E) Heart cross-sections were stained with H&E, indicating hypertrophic growth. (F) H&E staining indicating hypertrophic growth of cardiac myocytes, and WGA staining was performed to determine cell boundaries. (G) Quantification of cardiomyocyte cross-sectional areas in WGA staining in (F). (H–J) mRNA levels of the indicated hypertrophic fetal genes in WT and KLF11-Tg mice underwent Sham or TAC surgery. BNP, B-type natriuretic peptide. $n = 13$ in each group. $^{**}p < 0.01$ and $^{***}p < 0.0001$ *vs.* WT-Sham; $^{\#}p < 0.05$, $^{\#\#}p < 0.001$ and $^{\#\#\#}p < 0.0001$ *vs.* WT-TAC.

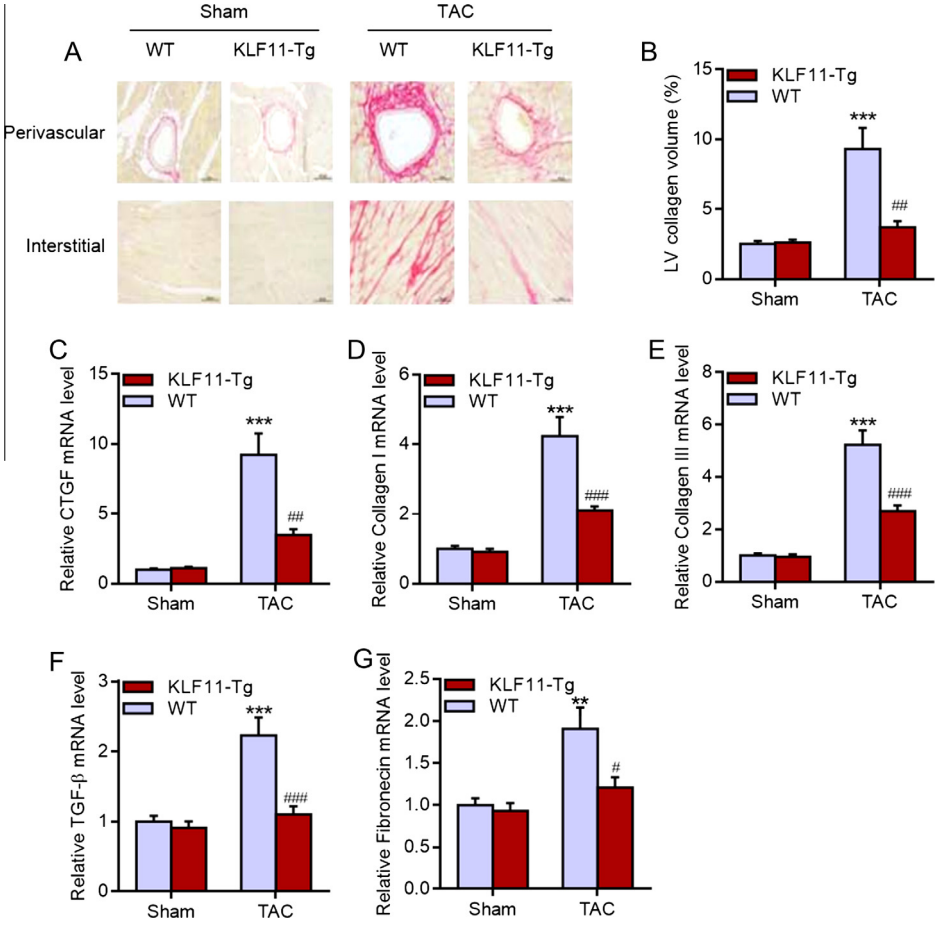

Fig. 4. KLF11 overexpression blocks TAC-induced cardiac fibrosis. (A) Heart sections of non-transgenic and KLF11 transgenic mice subjected to Sham or TAC treatment and picrosirius red staining to detect perivascular and interstitial fibrosis. (B) Quantification of myocyte cross-sectional area in non-transgenic and KLF11 transgenic mice subjected to Sham or to TAC treatment. (C–F) mRNA levels of the indicated fibrotic markers in heart samples from WT and KLF11-Tg mice underwent Sham or TAC surgery. CTGF, connective tissue growth factor; TGF-β, transforming growth factor. $n = 13$ per group. $^{***}p < 0.0001$ *vs.* WT-Sham; $^{\#}p < 0.05$, $^{\#\#}p < 0.001$ and $^{\#\#\#}p < 0.0001$ *vs.* WT-TAC.

the roles of KLFs in the heart are few. Overexpression of KLF4 in neonatal rat ventricular myocytes inhibits three cardinal features of cardiomyocyte hypertrophy: fetal gene expression, protein synthesis, and cell enlargement. Conversely, mice with cardiomyocyte-specific deletion of KLF4 are highly sensitized to TAC surgery and exhibit high rates of mortality [13]. In addition, KLF4 partly contributes to histone deacetylase inhibitors induced attenuation of cardiac hypertrophy [14,15]. In the heart, KLF5 is expressed primarily in cardiac fibroblasts and serves as a critical effector of angiotensin II signaling in these cells [16]. KLF5 expression can be induced by angiotensin II. Mice with KLF5 haplo-insufficiency show a blunted hypertrophic response to angiotensin II infusion with reduced cardiac mass, wall thickness, and cardiac fibrosis [16]. Furthermore, angiotensin II-mediated induction of TGF-β and collagen type IV are also blunted in KLF5 haplo-insufficient hearts [16]. Another KLF family member functioning in the heart is KLF15. Myocardial expression of KLF15 is reduced in rodent models of hypertrophy and in biopsy samples from patients with pressure-overload induced by chronic valvular aortic stenosis. KLF15-null mice are viable but, in response to pressure overload, develop an eccentric form of cardiac hypertrophy [17]. TGF-β-mediated activation of p38 MAPK is necessary and sufficient to decrease KLF15 expression. KLF15 robustly inhibits myocardin, a potent transcriptional activator. Loss of KLF15 during pathological LVH relieves the inhibitory effects on myocardin and stimulates the expression of serum response factor target genes, such as atrial natriuretic factor [18]. Elevation of cardiac KLF15 levels prevents the development of cardiac hypertrophy in a model of angiotensin II-induced hypertrophy [19]. In addition, KLF15 inhibits connective tissue growth factor (CTGF) expression in cardiac fibroblasts [20]. KLF13 is conserved across species and knockdown of KLF13 in *Xenopus* embryos leads to atrial septal defects and hypotrabeculation similar to those observed in humans or mice with hypomorphic GATA-4 alleles. Physical and functional interaction with GATA-4, a dosage-sensitive cardiac regulator, provides a mechanistic explanation for KLF13 action in the heart [21]. Clerk and colleagues [22] reported expression profiles of KLFs in response to endothelin (ET-1) stimulation in neonatal rat cardiomyocytes. When stimulated with ET-1, the expressions of KLFs 2, 4, 5, 6, 9, and 10 are induced rapidly and transiently, whereas the expressions of KLFs 3, 11, and 15 are down-regulated. Since ET-1 is a hypertrophic inducer, this observation is consistence with our finding that KLF11 is reduced in hypertrophic hearts.

KLF11 plays essential role in cardiovascular system. In this study, we found that KLF11 is down-regulated in hypertrophic hearts and overexpression of KLF11 blocked the TAC-induced development of cardiac hypertrophy in mice. KLF11 is expressed highly in vascular endothelial cells. KLF11 is a novel PPAR-γ co-regulator, which interacts with PPAR-γ and regulates its function in mouse cerebral vascular endothelial cells. KLF11 deficiency effectively abolishes cytoprotection of pioglitazone, an agonist of PPAR-γ, in mouse cerebral vascular endothelial cell cultures after oxygen–glucose deprivation, as well as pioglitazone-mediated cerebrovascular protection in a mouse middle cerebral artery

occlusion model [23]. Fenofibrate, a ligand of the PPAR-α, decreases ET-1 expression *via* transcriptional induction of the KLF11 repressor [24]. KLF11 is induced by pro-inflammatory stimuli in vascular endothelial cells. KLF11 overexpression inhibits expression of tumor necrosis factors-α-induced adhesion molecules. In contrast, KLF11 knockdown augments the pro-inflammatory status in ECs. KLF11 inhibits promoter activity of adhesion molecules induced by tumor necrosis factor-α and NF-κB p65 overexpression. Furthermore, KLF11$^{-/-}$ mice exhibit a significant increase in leukocyte recruitment to endothelial cells after lipopolysaccharide administration [25]. Since both NF-κB and ET-1 are positive regulators in the development of cardiac hypertrophy, the repression effect of KLF11 on those two factors may underline the mechanism by which KLF11 protects heart from hypertrophy. Taken together, KLF11 acts as an important orchestrator in cardiac and vascular function and homeostasis.

KLF11 is an important anti-fibrotic transcription factor. Previous reports have shown the function of KLF11 in preventing fibrosis in endometrium and liver [26,27]. Daftary et al. [26] identified a novel pathogenic role for KLF11 in preventing *de novo* disease-associated fibrosis in endometriosis. KLF11 binds to specific elements located in the promoter regions of key fibrosis-related genes from the Collagen, matrix metalloproteinase and TGF-β families in endometrial stromal cells. KLF11 binding resulted in transcriptional repression of those genes. In cultured mesenchymal cells, enhanced expression of KLF11 results in activated extracellular matrix pathways, including collagen gene silencing and matrix metalloproteinase activation without changes in tissue inhibitors of metalloproteinase. In addition, expression studies reveal decreased levels of KLF11 during liver fibrogenesis after chemically induced injury *in vivo*. Congruently, KLF11$^{-/-}$ mice, which should be deficient in the hypothesized anti-fibrogenic brake imposed by this transcription factor, display an enhanced response to liver injury with increased collagen fibril deposition [27]. In the present study, we found that KLF11 overexpression blunts perivascular and interstitial fibrosis, two markers indicating cardiac fibrosis. In addition, we showed that KLF11 inhibits the expression of a dozen of fibrotic genes. Taken together, KLF11 is an anti-fibrotic factor by repressing the transcription of fibrotic genes.

In summary, our study reveals an important role for the transcription factor, KLF11, in cardiac hypertrophy and fibrosis. Given the importance of negative transcription factors in cellular growth and fibrosis in cardiac hypertrophy and subsequent heart failure, these findings hold profound implications for understanding the heart response to hypertrophic stress as well as for the development of heart failure therapy.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bbrc.2013.12.024.

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