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Midkine exacerbates pressure overload-induced cardiac remodeling

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ABSTRACT

Midkine is a multifunctional growth factor, and its serum levels are increased with the functional severity of heart failure. This study aimed to examine the role of midkine in heart failure pathogenesis. Midkine expression levels were increased in the kidney and lung after transverse aortic constriction (TAC) surgery, but not sufficiently increased in the heart. After TAC, phosphorylation of extracellular signal-regulated kinase1/2 and AKT, and the expression levels of foetal genes in the heart were considerably increased in transgenic mice with cardiac-specific overexpression of midkine (MK-Tg) compared with wild-type (WT) mice. MK-Tg mice showed more severe cardiac hypertrophy and dysfunction, and showed lower survival rate after TAC than WT mice. We conclude that midkine plays a critical role in cardiac hypertrophy and remodelling.

1. Introduction

It is recognized that the presence of cardiovascular disease such as hypertension, myocardial infarction, and congestive heart failure increases the risk of kidney dysfunction [1]. In turn, the presence of chronic kidney disease has been associated with the deterioration of heart failure [2–4]. Therefore, the underlying mechanisms of how the heart and kidney interact during cardiac remodelling need to be determined.

Midkine, a heparin-binding growth factor with a molecular weight of 13 kDa, has various biological functions, such as for the growth of fibroblasts [5], survival of embryonic neurons [6], and migration of inflammatory cells [7], elicited through extracellular signal-regulated kinase (ERK) and AKT activation [6]. As midkine is strongly expressed in both the early and advanced stages of tumours and organs development [8,9], the involvement of midkine in the progression of carcinogenesis and the pathogenesis of cardiovascular disease has received attention [10,11].

In experimental models of ischemic heart disease, midkine was shown to decrease infarction size through its antiapoptotic effect and vasculogenesis [12,13]. Horiba et al. [14] reported that midkine was associated with vascular stenosis after intraluminal balloon injury through the recruitment of leucocytes and macrophages. Similarly, midkine expression is increased in the diabetic or ischemic kidney, and it induces tubulointerstitial inflammation [11,15].

We have previously reported that serum midkine levels are increased with the functional severity of congestive heart failure, and are independently associated with adverse cardiac events [16]. However, it remains to be determined whether midkine is associated with cardiac pathological hypertrophy and remodelling in pressure overloaded heart. For that purpose, we generated transgenic mice with cardiac-specific overexpression of midkine (MK-Tg) by using the α-myosin heavy chain (MHC) promoter, and examined the impact of midkine on cardiac hypertrophy induced by thoracic transverse aortic constriction (TAC).

2. Methods

2.1. Generation of MK-Tg mice

Human midkine cDNA was generated from A549 cells, and MK-Tg mice were created at Yamagata University by means of standard

Abbreviations: TAC, transverse aortic constriction; ERK, extracellular signal-regulated kinase; MHC, myosin heavy chain; PI3K, phosphatidylinositol 3-kinase; ANP, atrial natriuretic peptide; BNP, brain natriuretic peptide; CTGF, connective tissue growth factor; GAPDH, glyceraldehyde 3-phosphate dehydrogenase.

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techniques [17–20]. We confirmed the expression levels of midkine in the left ventricle by Western blotting (data not shown). MK-Tg mice and wild-type littermate (WT) mice with a C57/BL6 background were used in the present study. There were no considerable differences in phenotypic features, including general appearance, body weight, heart weight, wall thickness of the interventricular septum and posterior wall, left ventricular end-diastolic dimension (LVEDD), and left ventricular fractional shortening (LVFS) between the MK-Tg and WT mice at 8–12 weeks old (data not shown).

All experimental procedures were performed according to the animal welfare regulations, and the study protocol was approved by the Animal Subjects Committee of the Yamagata University School of Medicine. The investigation conformed to the *Guide for the Care and Use of Laboratory Animals* published by the US National Institutes of Health.

2.2. Pressure overload induced cardiac hypertrophy induced by TAC

TAC was performed to induce chronic pressure overload as described previously [21,22]. Briefly, mice (20–25 g body weight, 8–10 weeks old) were anesthetized by intraperitoneal injection with a mixture of ketamine (80 mg/kg) and xylazine (8 mg/kg), and intubated with a 20-gauge polyethylene catheter and ventilated with a rodent ventilator (Harvard Apparatus, Holliston, MA). The chest cavity was opened and the transverse section of the aorta was freed; an 8-0 prolene suture was passed around the aorta between the right innominate and left common carotid arteries; a tight ligature was tied against a 27-gauge needle; and the needle was then promptly removed.

2.3. Echocardiography

Transthoracic echocardiography was recorded under anaesthesia with an intraperitoneal injection of pentobarbital sodium (35 mg/kg), maintaining the heart rate at 450–500 beats/min, as described previously, using an FF sonic 8900 (Fukuda Denshi Co., Tokyo, Japan) [23,24].

2.4. Histological examination

After mice were euthanized, the heart was fixed with a 10% solution of formalin, embedded in paraffin, and then cut serially from the apex to the base. The sections were stained with haematoxylin-eosin or Masson's trichrome stain for histopathological analysis. Transverse sections were captured digitally, and the cardiomyocyte cross-sectional area was measured using a Scion imaging system (Scion, Frederick, MD) [22,23]. We traced the outline of at least 200 cardiomyocytes in each section, and the data were averaged. To assess the degree of fibrosis, the images from at least 10 fields for each heart were analysed as described previously [23,25].

2.5. Western blot analysis

Total proteins were extracted from the left ventricle, lung, and kidney with ice-cold lysis buffer as described previously [20,22]. Membranes were incubated with the following primary antibodies: anti-phospho-T202/Y204 and anti-total-ERK, anti-phospho-S473-AKT and total-AKT, β-tubulin (Cell Signaling Technology, Beverly, MA), and midkine (Sigma, St. Louis, MO). β-Tubulin was used as a loading control.

2.6. RT-PCR and real time RT-PCR

RT-PCR and real time RT-PCR were performed as described previously [19,26]. The primer sequences for midkine were as follows: forward 5′-GTGACTAAGCCCTGCACCTC-3′ and reverse 5′-ATCTCTTGTCCCTCCCCACT-3′, designed on the basis of GenBank sequences (NM_001012335.1). Primers for quantitative real-time RT-PCR were designed on the basis of GenBank sequences [atrial natriuretic peptide (ANP), K02781; brain natriuretic peptide (BNP), NM 008726; β-MHC, AY056464; α-MHC, M76601; collagen type I, NM007742; collagen type III, NM009930; connective tissue growth factor (CTGF), NM010217; and glyceraldehyde 3-phosphate dehydrogenase (GAPDH), NM001001303]. Amplification was performed using Light Cycler DNA Master SYBR Green I in a 20 μL volume reaction and analysed using Light Cycler Software ver.3.5 (Roche Diagnostics).

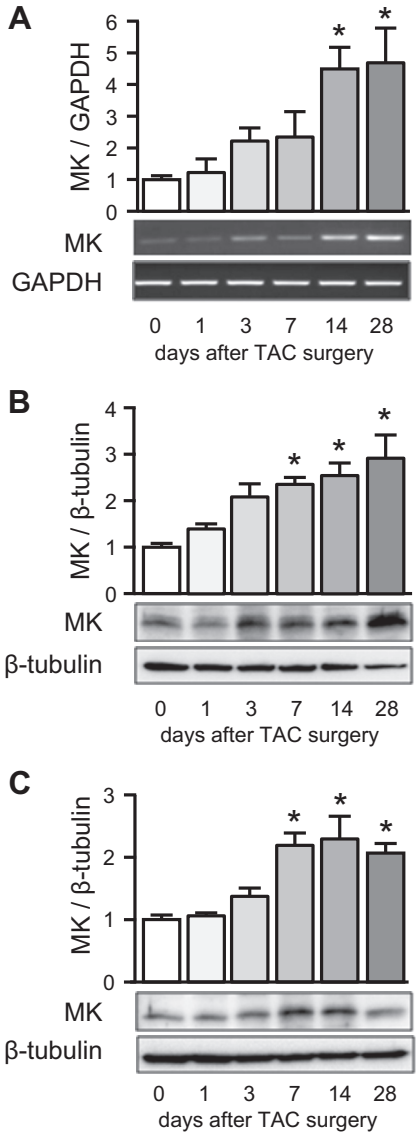

Fig. 1. Changes in midkine expression after TAC surgery. (A) mRNA expression of midkine in the heart of WT-TAC mice. Protein expression of midkine after TAC was confirmed in the kidney (B) and the lung (C). Expression levels were expressed as fold increase over the expression in WT control mice. $^{*}P < 0.05$ vs. control mice.

2.7. Statistical analysis

All values are expressed as mean ± the standard error of the mean (SEM). Differences between groups were evaluated using one-way analysis of variance with post hoc Bonferroni test. Survival curves after TAC were generated using the Kaplan–Meier method and compared using the log-rank test. A P value of <0.05 was considered statistically significant. Statistical analysis was performed with a standard statistical program package (JMP version 8; SAS Institute Inc., Cary, NC).

3. Results

3.1. MK expression levels in the heart, kidney, and lung after TAC

As we have previously reported that the circulating levels of midkine increased in heart failure patients, we tried to demonstrate whether midkine production changed in the process of heart failure. In the normal condition, midkine was observed to be expressed in the kidney and lung; however, the expression levels of midkine were faint in the heart. Sham operation did not change the midkine expression in the heart, kidney, and lung (data not shown). After pressure overload was induced, the mRNA expression levels of midkine in the heart were elevated from 3 days and peaked at 14 days (Fig. 1a). Interestingly, midkine protein expression was also increased in the kidney and the lung after pressure overload (Fig. 1b and c).

3.2. Effects of midkine overexpression on the phosphorylation of ERK1/2 and AKT in the heart after TAC surgery

We suspected that midkine released from kidney and lung might be involved in the pathogenesis of cardiac remodelling. To test this hypothesis, we performed TAC surgery in WT and MK-Tg mice, and the phosphorylation of ERK1/2 and AKT after pressure overload was investigated. We found that ERK1/2 and AKT were phosphorylated after TAC; moreover, the phosphorylation level in MK-Tg mice was higher than in WT mice, as shown in Fig. 2a ($P < 0.05$). Although the phosphorylation of p38 MAP kinase and c-Jun N-terminal kinase increased similarly after TAC, no difference was observed between the phosphorylation levels in MK-Tg and WT mice (data not shown).

3.3. Expression of foetal genes in hypertrophied hearts

We examined the mRNA expression of foetal genes by using real time RT-PCR. The expression levels of ANP, BNP, and β-MHC were considerably increased in the TAC group compared with the sham surgery group, and these increases were considerably enhanced in MK-Tg mice compared with WT mice (Fig. 2b).

3.4. Exacerbation of cardiac hypertrophy after TAC in MK-Tg mice

We performed histological examination to evaluate the cardiac hypertrophy induced by TAC. Fig. 4a shows representative transverse sections of WT and MK-Tg mice hearts after sham or TAC operation. The heart was considerably larger in MK-Tg mice than in WT mice at 4 weeks after TAC (Fig. 3a). MK-Tg mice exhibited considerable increases in heart weight-to-body weight ratio and left ventricular weight-to-body weight ratio compared with WT mice after TAC (Table 1). Microscopic analysis also revealed that the cross-sectional area of cardiomyocytes was considerably increased in MK-Tg mice compared with WT mice after TAC (Table 1).

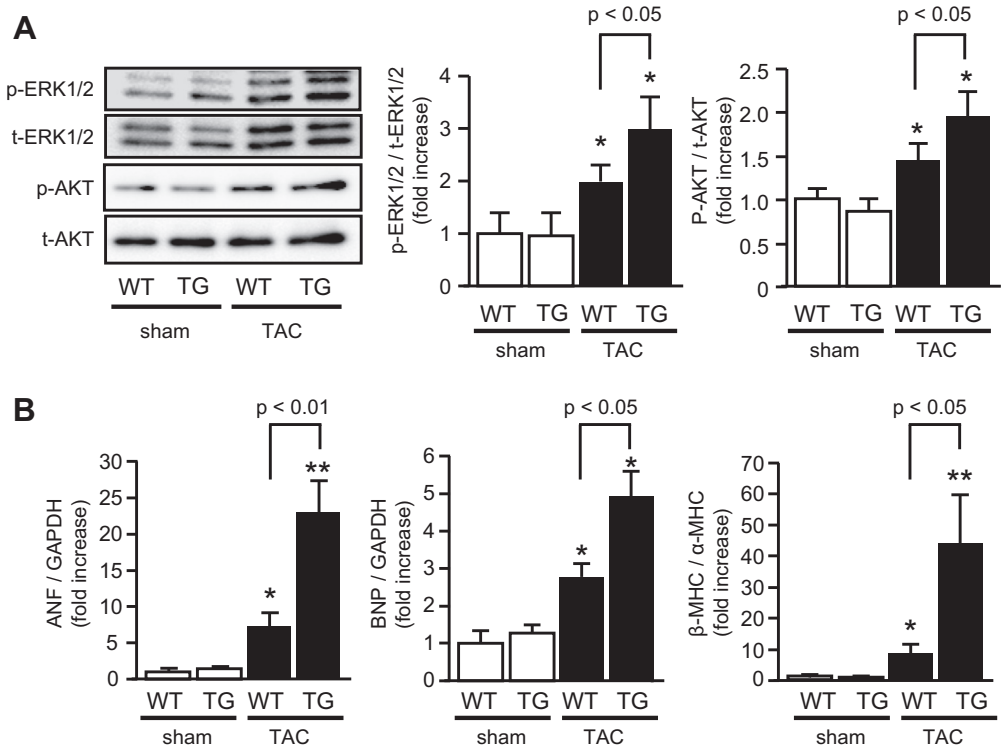

Fig. 2. (A) ERK1/2 and AKT phosphorylation after TAC. Representative Western blot and averaged protein levels for phospho-ERK1/2 and phospho-AKT. (B) Foetal gene expression after TAC. Quantitative analysis of ANF and BNP gene expression and β-MHC to α-MHC ratio using real-time PCR. Data are presented mean ± SEM ($n = 6$). Expression levels were expressed as fold increase over the expression in WT sham-operated mice. $^{*}P < 0.05$ and $^{**}P < 0.01$ vs. expression in WT sham-operated mice.

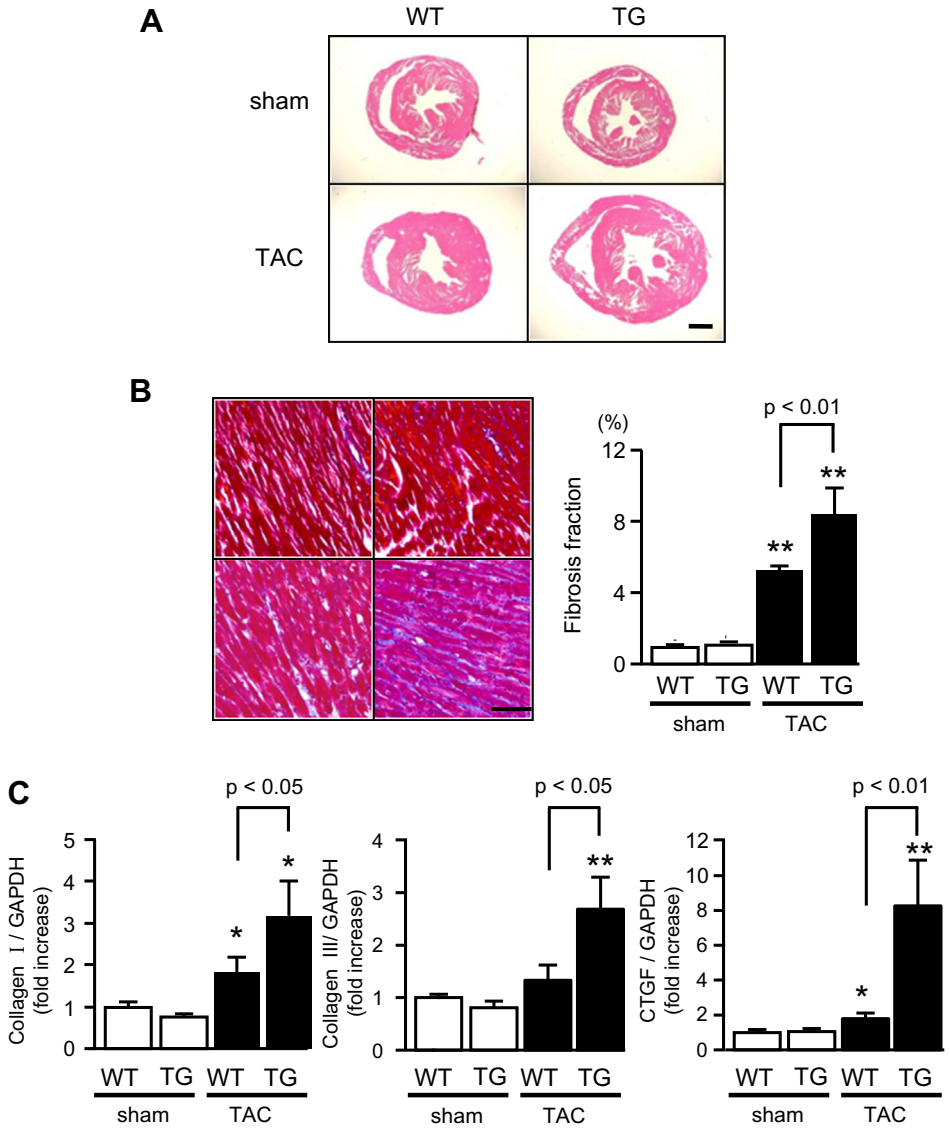

Fig. 3. Cardiac hypertrophy and fibrotic changes in MK-Tg mice after TAC. (A) Representative ventricular transverse sections after operation. Bar, 1 mm. (B) Representative histological micrographs of haematoxylin-eosin staining after operations. Bar, 20 μm. (C) Quantitative analysis of collagen type I and type III, and connective tissue growth factor mRNA gene expression ($n = 8$). Each expression level was normalized to the GAPDH level and expressed as fold increase over the level in the WT sham-operated mice. $^{**}P < 0.01$ vs. WT sham-operated mice.

3.5. Myocardial fibrosis and profibrotic gene expression

To examine whether pressure overload could induce distinct pathological differences between MK-Tg and WT mice after TAC, Masson trichrome staining was performed on heart sections to evaluate cardiac fibrosis. As shown in Fig. 3b, pressure overload induced more severe cardiac fibrosis in MK-Tg mice than in WT mice after TAC. We next examined the expression of collagen type I, collagen type III, and CTGF. The expression levels of these molecules after TAC were higher in MK-Tg mice than in WT mice (Fig. 3c).

3.6. Impaired cardiac function after pressure overload in MK-Tg mice

We observed that cardiac hypertrophy and fibrosis were enhanced in MK-Tg mice, and we suspected that cardiac function was attenuated in MK-Tg mice compared with WT mice. Representative M-mode echocardiograms at 4 weeks after operation are shown in Fig. 4a. As we expected, MK-Tg mice showed a greater LVEDD with decreasing LVFS compared with WT mice after TAC (Table 1). The persistent pressure overload induced congestive heart failure, which was manifested by a lower survival rate up to 4 weeks after TAC in MK-Tg mice than in WT mice (50% vs. 76%, $P < 0.05$), as shown in Fig. 4b. These results suggested that MK-Tg mice showed cardiac hypertrophy and dysfunction after pressure overload.

4. Discussion

In the present study, we demonstrated the critical role of increased expression of midkine in the development of cardiac hypertrophy and heart failure. After induction of pressure overload, midkine expression was increased mainly in the lung and the kidney. Phosphorylation of ERK1/2 and AKT in the heart after pressure overload was considerably increased in MK-Tg mice compared with WT mice. At 4 weeks after TAC, MK-Tg mice showed more severe left ventricular hypertrophy and fibrotic change than WT mice. The expression levels of cardiac foetal genes were considerably increased in MK-Tg mice compared with WT mice after

Table 1
Gravimetric data and cardiac function (echocardiographic and cardiac catheter) after TAC or sham operation.

	WT-sham	Tg-sham	WT-TAC	Tg-TAC
BW (g)	26.5 ± 0.7	25.8 ± 0.8	25.0 ± 0.5	24.8 ± 0.6
HW/BW (mg/g)	4.46 ± 0.12	4.89 ± 0.27	6.47 ± 0.45*	8.24 ± 0.56**,#
LVW/BW (mg/g)	3.05 ± 0.12	3.64 ± 0.21	4.98 ± 0.20**	7.36 ± 0.23**,##
Cross sectional area (μm^2)	194 ± 9	234 ± 32	307 ± 33**	359 ± 23**,##
Echocardiographic data				
IVS (mm)	0.79 ± 0.04	0.79 ± 0.03	1.09 ± 0.06**	0.98 ± 0.03**
PW (mm)	0.93 ± 0.03	0.87 ± 0.05	1.10 ± 0.07	0.97 ± 0.10
LVEDD (mm)	2.73 ± 0.08	2.87 ± 0.04	3.36 ± 0.11**	4.06 ± 0.14**,##
LVFS (%)	43.2 ± 0.7	40.5 ± 1.1	35.1 ± 2.5*	20.3 ± 2.0**,##
HR (bpm)	449 ± 24	421 ± 15	428 ± 10	431 ± 47

Data are presented as mean ± SEM (n = 8–10). TAC, transverse aortic constriction; LVW, left ventricular weight; left ventricular weight; IVS, interventricular septum; PW, posterior wall; LVEDD, left ventricular end-diastolic dimension; LVFS, left ventricular fractional shortening; HR, heart rate, respectively.
* $P < 0.05$ vs. sham-operated WT mice.
** $P < 0.01$ vs. sham-operated WT mice.
# $P < 0.05$ vs. WT-TAC mice.
$P < 0.01$ vs. WT-TAC mice.

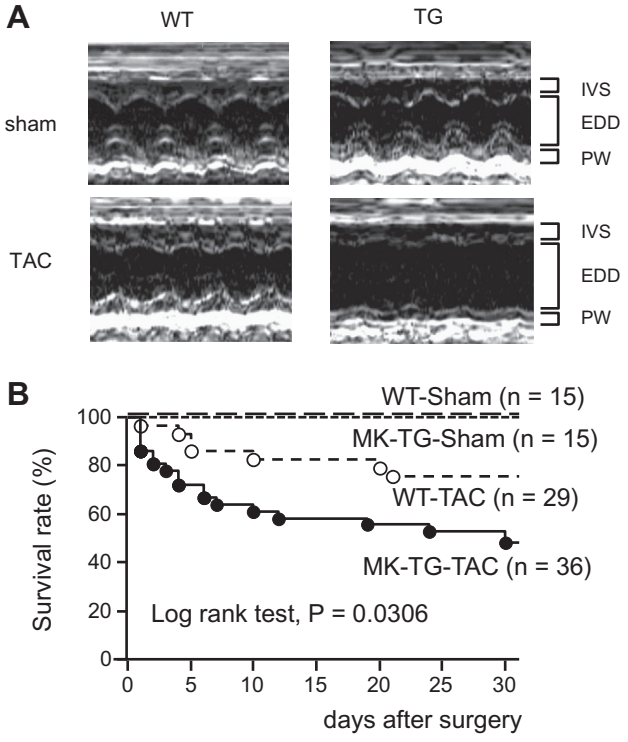

Fig. 4. Cardiac dysfunction in MK-Tg mice after TAC. (A) Representative echocardiograms in MK-Tg and WT mice at 4 weeks after surgery. (B) Survival curves in HMGB1-Tg and WT mice after TAC or sham operation.

TAC operation, and cardiac dysfunction was more severe in MK-Tg mice than in WT mice. These data suggest that overexpression of midkine deteriorates the cardiac hypertrophic response induced by pressure overload and results in the development of heart failure.

Nevertheless, even with existing pharmacological therapies, the incidence of heart failure is still increasing [27]. Current medical treatments for the prevention of cardiac hypertrophy rely on pharmacologic blockade of receptors that respond to neuroendocrine stimuli [28]. Therefore, it is believed that direct and indirect interactions between the heart and the kidney can initiate the pathophysiological linkage [2,4,29]. We have previously shown that the circulating level of midkine is independently associated with the severity and onset of cardiac events in patients with heart failure [16]. However, the mechanisms by which serum levels of midkine increase in heart failure patients are unknown. Midkine is most intensely expressed during midgestation, whereas the expression is weak or absent in most normal adult tissues except the kidney. Reynolds et al. [30] reported that hypoxia induces midkine expression through the binding of hypoxia inducible factor-1α in adult mice. Moreover, Hobo et al. [31] reported that 5/6 nephrectomy induces midkine expression in the kidney and lung. In the present study, after TAC operation, protein levels of midkine were increased in the kidney and the lung, but were not substantially increased in the heart. The maximum increase in midkine expression occurred at 14–28 days after TAC (Fig. 1). Therefore, midkine expression in the kidney and the lung induced by TAC may be associated with organ hypoxia accompanying cardiac hypertrophy and cardiac dysfunction. Considering these results, midkine secreted from the kidney and lung may be associated with cardio–renal interaction.

Although midkine levels were increased in the kidney and lung, the role of midkine on the pathogenesis of heart failure after pressure overload has not been evaluated. In the present study, cardiac-specific overexpression of midkine exacerbates cardiac dysfunction and pathological remodelling in mice with pressure overload-induced heart failure. Previous studies showed that midkine had a cardioprotective effect in experimental ischemic heart models. Midkine-deficient mice showed larger infarct size than did WT mice after ischemia/reperfusion and myocardial infarction [12,13,32]. Midkine has various biological effects, including cell survival, migration, and neurite outgrowth [33]. These cardioprotective effects of midkine might be elicited by the activation of antiapoptotic signals and promotion of angiogenesis [12,13]. Previously, the antiapoptotic effect and angiogenesis induced by midkine were reported to be associated with the activation of ERK and phosphatidylinositol 3-kinase (PI3K)/AKT. However, it is also recognized that the ERK and PI3K/AKT pathways are involved in cardiac hypertrophy induced by mechanical stress [34,35]. ERK1/2 becomes activated in cardiomyocytes in response to G protein-coupled receptor agonists, receptor tyrosine kinase agonists, cytokines, and stretch, and is involved in cardiac hypertrophy [36]. Moreover, several growth factors bind to their membrane-bound tyrosine kinase receptors and activate a 110-kDa lipid kinase PI3K/AKT pathway [34], which was associated with not only physiological hypertrophy but also maladaptive hypertrophy [34,35]. Therefore, it is suspected that increased levels of midkine enhanced the activation of the ERK1/2 and AKT pathways after pressure overload, and induced cardiac hypertrophy and heart failure. This hypothesis was supported by the fact that phosphorylation of ERK1/2 and AKT considerably increased in the hearts of MK-Tg

mice compared with WT mice after TAC (Fig. 2). Increasing levels of midkine have cardioprotective effects on experimental models of ischemic heart disease through antiapoptotic effect and angiogenesis; however, these also have adverse effects on cardiac hypertrophy induced by chronic pressure overload. These results suggest a crucial role of midkine as a novel therapeutic target for heart failure.

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