Pravastatin slows the progression of heart failure by inhibiting the c-Jun N-terminal kinase-mediated intrinsic apoptotic signaling pathway

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Abstract. Tumor necrosis factor-α (TNF-α) and c-Jun N-terminal kinases (JNKs) are known to be associated with apoptosis and are important in cardiac remodeling. It remains to be determined whether statins inhibit cardiac remodeling through interfering with TNF-α-JNK-related signaling pathways. This study was designed to investigate the effect of pravastatin on the progression of hypertrophy to heart failure in transverse aortic constriction (TAC) and the associations with TNF-α-JNK signaling. Either pravastatin (5 or 20 mg/kg/day) or vehicle was orally administered to male C57BL/6J mice with TAC. Cardiac remodeling and left ventricular hemodynamics, as well as JNK-dependent apoptotic signals were analyzed 4 weeks following TAC. Neonatal rat cardiomyocytes were cultured to investigate the effect of pravastatin on TNF-α-induced JNK-related apoptotic signals. Notably, pravastatin reduced the heart/body weight and lung/body weight ratios. In addition, a decrease of left ventricular (LV) echocardiographic dimensions, an increase of LV fractional shortening and diastolic index, a reduction of JNK activity, caspase-12 and Bax were observed in the pravastatin-treated groups. The TNF-α-induced phosphorylation of JNK and upregulation of caspase-12 and Bax in cultured cardiomyocytes was inhibited by pravastatin. These results indicated that pravastatin attenuates cardiac remodeling by inhibiting JNK-dependent pro-apoptotic signaling.

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Abbreviations: CHF, chronic heart failure; CHOP, C/EBP homologous protein; ER, endoplasmic reticulum; TAC, transverse aortic constriction; TNF-α, tumor necrosis factor-α; JNK, c-Jun N-terminal kinase; LVPWd, left ventricular posterior wall diastolic thickness; LVEDd, LV end-diastolic diameter; LVESd, LV end-systolic diameter; LVFS, LV fractional shortening; LVEF, LV ejection fraction

Key words: pravastatin, cardiomyocyte, hypertension, heart failure, c-Jun N-terminal kinase, apoptosis

Introduction

Cardiac hypertrophy frequently progresses into chronic heart failure (CHF). Slowing or reversing cardiac remodeling is an important therapeutic goal in patients with CHF. Studies have shown that hydroxymethylglutaryl-CoA reductase inhibitors (statins) attenuate cardiac remodeling in animals or patients with either ischemic or non-ischemic CHF (1-7), suggesting that statin therapy may be a potential novel approach for CHF. A meta-analysis of randomized controlled trials showed that treatment with statins in CHF patients attenuates cardiac remodeling and relives clinical symptoms (8).

Pleiotropic effects of statins have been extensively investigated; however, the involvement of statins in extrinsic and intrinsic apoptosis pathways during CHF remains largely unknown. We previously demonstrated that pressure overload induced prolonged endoplasmic reticulum (ER) stress, which contributes to cardiomyocyte apoptosis during the progression of cardiac hypertrophy to CHF (9). In addition, we demonstrated that the inhibition of cardiac remodeling by statins is associated with amelioration of ER stress-initiated apoptosis via decreasing the expression of C/EBP homologous protein (CHOP) (1). When ER stress is prolonged, however, initiation of the apoptotic processes is promoted by CHOP and also by the activation of c-Jun N-terminal kinases (JNK)- and/or caspase-12-dependent pathways (10). The intrinsic apoptotic signaling pathway may be initiated by mitochondrial events and/or the ER (11,12). Pro-apoptotic proteins, caspase-12 and Bax, are closely associated with mitochondrial events and ER stress during apoptosis. Bax is phosphorylated by stress-activated c-Jun N-terminal kinase (JNK), which leads to mitochondrial translocation prior to apoptosis (13). The extrinsic apoptosis pathway initiated by tumor necrosis factor α (TNF-α) is critical in CHF and the receptor (extrinsic) and the mitochondrial (intrinsic) pathway are interconnected at different levels. However, it remains unknown whether or not statins inhibit cardiac remodeling through interfering with the TNF-α-JNK related signaling pathway.

Therefore, it was hypothesized that pravastatin delayed the progression of cardiac hypertension to CHF by inhibiting the JNK-mediated apoptotic signal pathway. To confirm this hypothesis, the involvement of pravastatin on the intrinsic pro-apoptotic proteins, caspase-12 and Bax, *in vivo* and *in vitro* was investigated. Furthermore, as JNK is important in the intrinsic apoptotic signaling pathway, the effect of pravastatin on JNK in mouse hearts subjected to TAC and cultured cardiomyocytes stimulated by TNF-α were analyzed.

Materials and methods

Animal models and experimental protocols. All procedures were conducted in male C57BL/6J mice (age, 7-8 weeks; weight, 20-24 g, provided by the Animal Center of Southern Medical University), were approved by the Animal Care and Use Committee of the Southern Medical University (Guangzhou, Guangdong, China) and were in accordance with the Guide for the Care and Use of Laboratory Animals published by the US National Institutes of Health (NIH publication no. 85-23, revised 1996).

C57BL/6J mice were anesthetized with a combination of ketamine (100 mg/kg) and xylazine (5 mg/kg) via intraperitoneal injection. Transverse aortic constriction (TAC) surgery was performed as previously described (14,15). Pravastatin (Pra, 5 or 20 mg/kg, dissolved in 0.9% saline; provided by Daiichi-Sankyou Pharmaceutical Co. Ltd., Tokyo, Japan) was orally administered from the third day post-surgery. The mice were divided into four groups: Sham-operated (n=7), TAC (n=8), TAC + Pra5 (n=5) and TAC + Pra20 (n=6) groups. Mice were sacrificed by anesthesia overdose with 150 mg/kg pentobarbital sodium intraperitoneal and cervical dislocation following analysis of cardiac functions and hypertrophy with echocardiography and invasive left ventricular (LV) hemodynamic assessment 4 weeks after TAC. The hearts and lungs were harvested and weighed. The hearts and lungs used for western blot analysis were snap-frozen in liquid nitrogen and stored at -80˚C.

Echocardiography. Transthoracic echocardiography was performed with a Sonos 4500 and a 15-6 L MHz transducer (Philips, Eindhoven, The Netherlands). Images were standardized to short axis view at the LV mid-papillary level and the posterior wall diastolic thickness (LVPWd), LV end-diastolic diameter (LVEDd) and LV end-systolic diameter (LVESd) were recorded. LV systolic function was also assessed from these measurements by calculating the LV fractional shortening (LVFS) and the LV ejection fraction (LVEF).

Hemodynamic measurement. Pressure overload was confirmed by measuring the gradient in carotid artery pressure by invasive hemodynamic assessment; the systolic blood pressure gradient was identified to be similar between TAC and TAC with pravastatin groups. For LV hemodynamic assessment, mice were anesthetized, intubated and ventilated. A Millar catheter (Millar Instruments, Inc., Houston, TX, USA) was inserted into the right carotid artery and advanced into the LV cavity. LV systolic pressure (LVSP) and the LV end-diastolic pressure (LVEDp) were recorded. The maximum and minimum rates of LV pressure change (dP/dt max and dP/dt min, respectively), as well as contractility index (max dp/dt divided by corresponding LV pressure) and diastolic index (min dp/dt divided by corresponding LV pressure) were calculated using using PowerLab software (blood pressure module, ADInstruments Shanghai Trading Co, Shanghai, China).

Neonatal cardiomyocyte culture. Ventricular myocytes were prepared from Sprague-Dawley rats (age, 1-2 days) obtained from the Animal center of Southern Medical University. In brief, the rats were sacrificed by 2% isoflurane inhalation and cervical dislocation. The hearts were quickly excised and immediately embedded in freezing Hank's solution. Cardiomyocytes were dispersed by digestion with 0.1% trypsin and 0.03% collagenase at 37˚C, then were collected after differential adhesion of non-cardiomyocytes and plated at a density of 150-200 cells/mm^2. Cardiomyocytes were incubated for 72 h in Dulbecco's modified Eagle's medium supplemented with 10% fetal calf serum and then grown for 24 h under serum-free conditions. Pravastatin (10 μM) was added 2 h prior to the addition of 10 ng/ml TNF-α.

Western blot analysis. Protein samples were prepared from whole-heart homogenates or cultured cardiomyocytes. A total quantity of 30 μg of each sample was separated on 5-15% gradient polyacrylamide gels. When transferred onto nitrocellulose membranes, the membranes were incubated with primary antibodies against caspase-12, JNK, phospho-JNK, Bax and glyceraldehyde 3-phosphate dehydrogenase (GAPDH; Santa Cruz Biotechnology, Inc., Santa Cruz, CA, USA) followed by incubation with horseradish peroxidase-conjugated secondary antibodies (Santa Cruz Biotechnology, Inc.). The bound antibody was detected by the enhanced chemiluminescence method according to the manufacturer's instructions (Amersham Bioscience, Buckinghamshire, UK) and band intensities were quantified by the use of NIH image software (Image J 1.42q; NIH, Bethesda, MD, USA).

Statistical analysis. All data are presented as the mean ± SE. $P<0.05$ was considered to indicate a statistically significant difference. Unpaired Student's t-test was used for comparisons between two groups and one-way analysis of variance with post hoc analysis using the Tukey-Kramer test was used for multiple comparisons.

Results

Pravastatin attenuates cardiac remodeling. It was demonstrated that pravastatin improved cardiac remodeling and dysfunction induced by TAC (Fig. 1A). Prior to TAC, the LV wall thickness and dimensions were similar in the four groups of mice (data not shown). TAC induced significant LV hypertrophy and dilation (Fig. 1B and C). Four weeks following TAC, the heart became larger and the heart weight/body weight ratio increased significantly compared with the sham-operated group (Fig. 1D and E). LV wall thickness (Fig. 1B) and dimensions (Fig. 1C), measured by echocardiography, were greater in the TAC group compared with the sham-operated group. Pravastatin treatment significantly

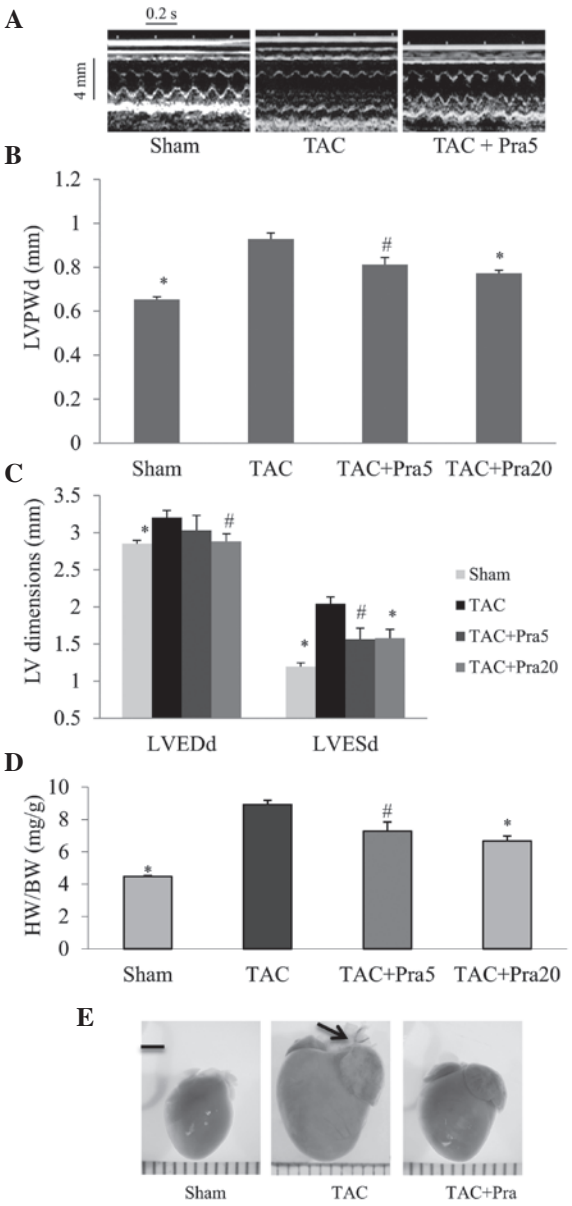

Figure 1. Effects of pravastatin on cardiac remodeling 4 weeks following surgery. (A) Representative echocardiograms of the LV in sham, TAC and TAC + pravastatin 5 and 20 mg/kg/d groups (Pra5 and Pra20, resepctively). (B) Results of LVPWd. (C) LV dimensions (LVEDd and LVESd). (D) HW/BW ratio. (E) Representative images of the heart from different groups. Scale bar, 2 cm. Arrows indicate banding site of aortic arch. n=8 in sham and TAC groups, n=6 in TAC + Pra5 and Pra20 groups, respectively for Fig. 1B and C; n=7, 8, 6 and 6 in the respective groups for Fig. 1D. *P<0.01 and #P<0.05 vs. the TAC group. LV, left ventricle; TAC, transverse aortic constriction; LVPWd, left ventricular posterior wall diastolic thickness; LVEDd, left ventricular end-diastolic diameter; LVESd, left ventricular end-systolic diameter; HW, heart weight; BW, body weight.

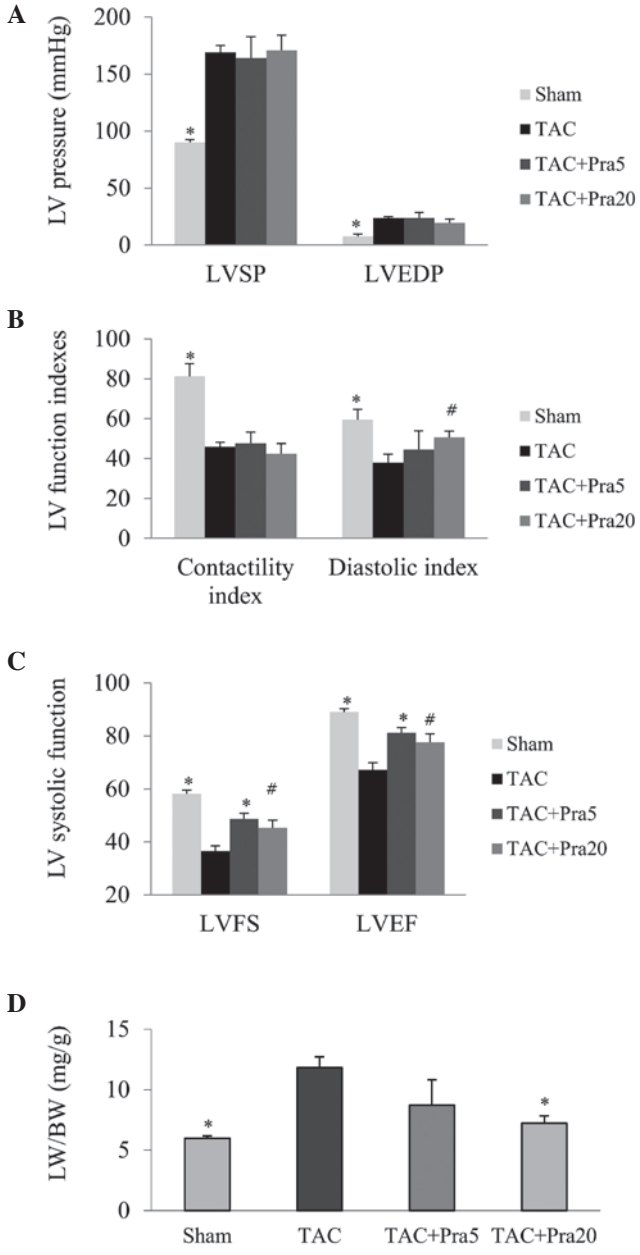

Figure 2. Effects of pravastatin on cardiac function 4 weeks following surgery. (A) Left ventricular peak systolic and end-diastolic pressure measured by using a Millar catheter. (B) LV contractility and diastolic indices. (C) LV systolic function (LVFS and LVEF) analyzed by echocardiography. (D) Pulmonary congestion determined by the LW/BW ratio. *P<0.01 and #P<0.05 vs. the TAC group; n=7, 8, 5 and 6 in the sham, TAC, TAC + Pra5 and TAC + Pra20 groups, respectively for Fig. 2A and B; n=8, 8, 6 and 6 in the respective groups for Fig. 2C; and n=7, 8, 6 and 6 in the respective group for Fig. 2D. LVSP, left ventricular peak systolic pressure; LVEDP, left ventricular end-diastolic pressure; LVFS, LV fractional shortening; LVEF, LV ejection fraction; LW/BW, lung weight/body weight; TAC, transverse aortic constriction.

inhibited LV hypertrophy and dilation in a dose-dependent manner (Fig. 1A-E).

Pravastatin improves heart failure. Heart function was analyzed by echocardiography, LV hemodynamics and pulmonary congestion. The hemodynamic measurements obtained 4 weeks after TAC, confirmed that LV pressure was significantly increased and LV function indexes were decreased, as systolic function evaluated by dP/dt max, ratio of dP/dt max to instantaneous pressure and diastolic function by dP/dt min, ratio of dP/dt min to instantaneous pressure (Fig. 2A-C). Pravastatin treatment did not significantly decrease LV pressure or increase LV systolic function, but improved LV diastolic function, as reflected by LVEDP and diastolic index (P<0.05; Fig. 2A and B). FS and EF, parameters of LV systolic function, decreased significantly in the TAC group compared with the sham group. The lung weight/body weight (LW/BW) ratio, an index of pulmonary congestion, was markedly higher in TAC

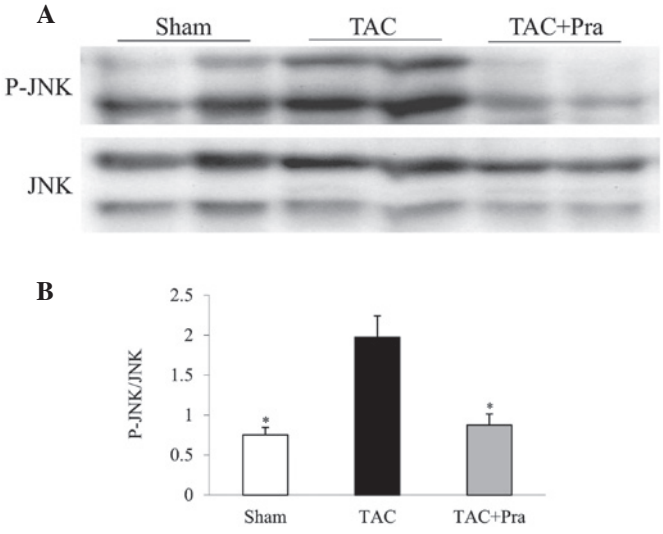

Figure 3. Effects of pravastatin on protein expression of JNKs and phosphorylation of JNK (p-JNK) in whole hearts 4 weeks following surgery. (A) Representative results of western blot analysis. (B) Quantitation of phospho-JNK relative to JNK. *P<0.01 and #P<0.05 vs. the TAC group, n=3 per group. JNKs, c-Jun N-terminal kinases; TAC, transverse aortic constriction; Pra, pravastatin.

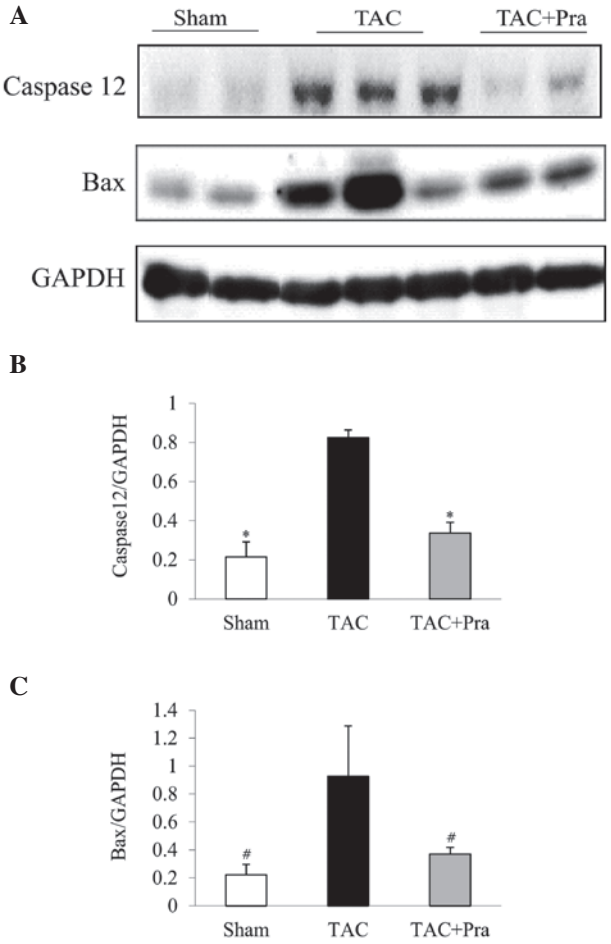

Figure 4. Effects of Pra on protein expression of caspase-12 and Bax in whole hearts 4 weeks following surgery. (A) Western blot analysis results of caspase-12, Bax and loading control GADPH. (B) Quantitation of caspase-12 or (C) Bax relative to GAPDH. *P<0.01 and #P<0.05 vs. the TAC group, n=3 in each group. Pra, pravastatin; GADPH, glyceraldehyde 3-phosphate dehydrogenase; TAC, transverse aortic constriction.

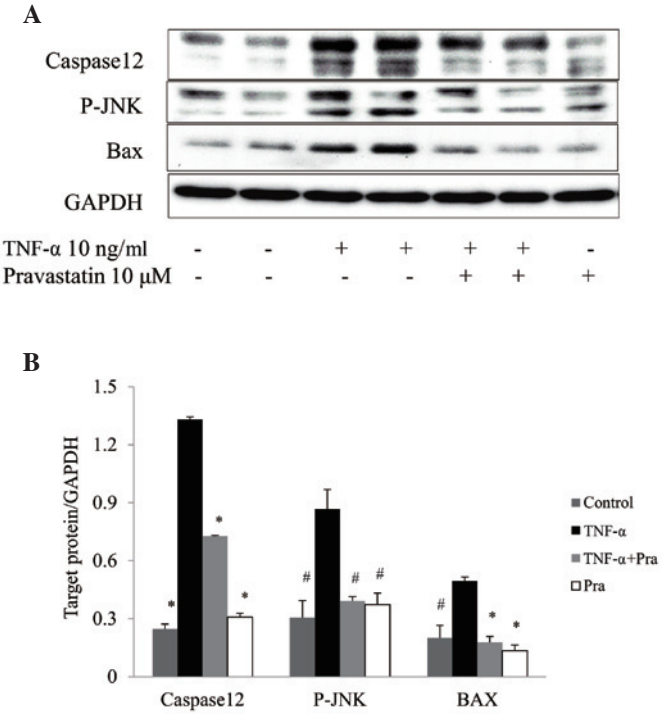

Figure 5. Effects of pravastatin on protein expression of caspase-12, phospho-JNK (p-JNK) and Bax in cultured neonatal rat cardiomyocytes stimulated with TNF-α. (A) Representative images of western blot analysis using GADPH as a reference; (B) Quantitation of caspase-12, phospho-JNK and Bax. *P<0.01 and #P<0.05 vs. the TNF-α group, n=4 per group. TNF-α, tumor necrosis factor-α; GADPH, glyceraldehyde 3-phosphate dehydrogenase.

mice than in sham-operated mice, while pravastatin-treated TAC mice exhibited a significantly higher FS and EF as well as a lower LW/BW ratio (P<0.05 or P<0.01; Fig. 2C and D).

Pravastatin inhibits JNK phosphorylation in vivo. As JNK is important in the intrinsic pro-apoptotic signaling pathway, it was investigated whether pravastatin influences the JNK signaling pathway in TAC mice. It was demonstrated that the ratio of phosphorylated-JNK to JNK was significantly greater in the TAC mice than in the sham-operated group, while treatment with pravastatin markedly decreased the activity of JNK (Fig. 3A and B).

Pravastatin reduces the protein expression levels of caspase-12 and Bax in vivo. As shown in Fig. 4, the protein expression of caspase-12 and Bax was significantly higher four weeks following TAC compared with the sham-operated group; while pravastatin treated TAC mice exhibited significantly lower expression levels of these apoptosis-related proteins.

Pravastatin inhibits the apoptosis signaling pathway in cultured cardiomyocytes. In cultured neonatal rat cardiomyocytes, treatment with TNF-α for 24 h significantly activated intrinsic apoptotic signaling, as determined by the increase of caspase-12 and Bax proteins, and the activity of JNK. Co-treatment with 10 μM pravastatin markedly decreased the expression of these apoptosis-related proteins and also downregulated the expression of phosphorylated-JNK (Fig. 5A and B). Thus, TNF-α is

involved in cardiac molecular and cellular changes during TAC and is associated with heart failure.

Discussion

This study demonstrated that pravastatin exerts cardioprotection against cardiac remodeling by the inhibition of the JNK-dependent intrinsic pro-apoptotic signaling pathway in TAC mice, which supports the hypothesis that inhibition of JNK phosphorylation is a potential therapeutic target for slowing the progression of hypertrophy to heart failure.

JNK, a predominant branch of the mitogen-activated protein kinase signaling cascades, has been implicated in the pathophysiology of cardiac hypertrophy and heart failure (16,17). Myocardial JNK1/2 is activated by inflammatory cytokines, oxidant stress, G protein-coupled receptors and ER stress (18-24), and all of which are associated with myocardial hypertrophy and heart failure. To the best of our knowledge, the involvement of JNK in cardiac remodeling and cardiomyocyte apoptosis remains controversial (17). Previous studies have clearly established the involvement of JNK in TNF-α-induced apoptosis, stimulating the release of cytochrome *c* from mitochondria through an analogous pathway involving the proapoptotic proteins Bid and Bax. Moreover, JNK may be activated prior to or following the induction of ER stress and then induces the activation of caspase-12, which is central in ER stress-induced apoptosis (25-28). The activation of JNK and caspase-12 is associated with the TNF receptor associated factor-2, while TNF-α is an important therapeutic target of statins (29). However, it remains to be determined whether statins improve cardiac remodeling thorough the modulation of TNF-α associated apoptosis initiated at the ER and mitochondria.

In the present study, pravastatin was observed to significantly inhibit the activation of JNK and the upregulation of pro-apoptotic proteins Bax and cleavage caspase-12 in TAC hearts and TNF-α stimulated cardiomyocytes. JNK has been shown to be critical for the release of cytochrome *c* from mitochondria (30), and may also be essential for ER stress-induced cardiomyocyte apoptosis. Bax and caspase-12 may be stimulated by JNK in cardiomyocytes. The activated Bax forms membrane channels through which cytochrome *c* is released (31), while caspase-12 was demonstrated to be critical in response to ER stress-induced apoptosis (25).

An increasing number of studies suggest that apoptosis may be a key modulator in the transition from compensatory hypertrophy to heart failure. Mitochondrial dysfunction and ER stress are demonstrated to be involved in the intrinsic apoptosis signaling pathway. Caspase-12 and Bax are two important proteins, which indicate ER stress and mitochondrial events respectively during cardiomyocyte apoptosis. The results of the present study demonstrated that caspase-12 and Bax in TAC mice were inhibited by pravastatin. Also, in cultured cardiomyocytes, pravastatin was shown to inhibit TNF-α-induced caspase-12 and Bax, which may contribute to cardiomyocyte hypertrophy. TNF-α, a proinflammatory cytokine, induces cardiomyocyte hypertrophy, migration, apoptosis and necrosis, which results in ventricular remodeling and heart failure (32). The results demonstrated that pravastatin inhibits cardiac remodeling and improves cardiac function via regulating TNF-α associated JNK-dependent intrinsic apoptosis signaling and thus slows the progression of hypertrophy to heart failure. This may suggest the use of JNK-targeted drugs as an alternative therapeutic strategy for patients with cardiac hypertrophy and heart failure.

In conclusion, the results of this study indicate that pravastatin attenuates cardiac remodeling by inhibiting JNK-dependent pro-apoptotic signaling.

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