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The histone acetyltransferase MOF overexpression blunts cardiac hypertrophy by targeting ROS in mice

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ABSTRACT

Imbalance between histone acetylation/deacetylation critically participates in the expression of hypertrophic fetal genes and development of cardiac hypertrophy. While histone deacetylases play dual roles in hypertrophy, current evidence reveals that histone acetyltransferase such as p300 and PCAF act as pro-hypertrophic factors. However, it remains elusive whether some histone acetyltransferases can prevent the development of hypertrophy. Males absent on the first (MOF) is a histone acetyltransferase belonging to the MYST (MOZ, Ybf2/Sas3, Sas2 and TIP60) family. Here in this study, we reported that MOF expression was down-regulated in failing human hearts and hypertrophic murine hearts at protein and mRNA levels. To evaluate the roles of MOF in cardiac hypertrophy, we generated cardiac-specific MOF transgenic mice. MOF transgenic mice did not show any differences from their wide-type littermates at baseline. However, cardiac-specific MOF overexpression protected mice from transverse aortic constriction (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 observed lower expression of hypertrophic fetal genes in TAC-challenged MOF transgenic mice compared with that of wide-type mice. Mechanically, MOF overexpression increased the expression of Catalase and MnSOD, which blocked TAC-induced ROS and ROS downstream c-Raf-MEK-ERK pathway that promotes hypertrophy. Taken together, our findings identify a novel anti-hypertrophic role of MOF, and MOF is the first reported anti-hypertrophic histone acetyltransferase.

1. Introduction

Presently, heart failure has been one of the leading causes of morbidity and mortality worldwide. Cardiac hypertrophy is one of the most important pathological bases of heart failure [1]. Cardiac hypertrophy is a common response of cardiomyocytes to physiology and pathological stimuli. Because mammalian cardiomyocytes fail to divide soon after birth, hypertrophy is the only way for them to response to the increased workload. During cardiac hypertrophy, not only the cell size is increased in cardiomyocytes, but the sarcomeres are added and reorganized, and a group of genes that are usually expressed during fetal heart development are re-expressed. These alterations are compensatory system of the heats initially to deal with the increased workload on the heart. However, sustained hypertrophy would result in congestive heart failure and sudden death due to arrhythmias [1,2].

At the molecular level, hypertrophy of cardiomyocytes is an outcome of imbalance between pro-hypertrophic and anti-hypertrophic factors and their downstream mechanisms controlling cell growth [2]. Accumulating studies have revealed a key role of histone acetyltransferases (HATs) and deacetylases (HDACs) in the controlling of cardiac hypertrophy. HDACs of different classes have been shown to have different effects on cardiac growth. HDAC2 of the class I HDAC regulates expression of many fetal cardiac isoforms. HDAC2 deficiency or chemical HDAC inhibition prevented the re-expression of fetal genes in hearts and attenuated cardiac hypertrophy when exposed to hypertrophic stimuli [3]. In contrast, class IIa HDACs, such as HDAC5 and HDAC9, function as signal-responsive repressors of cardiac hypertrophy by inactivating MEF2 [4–6]. For the NAD^+-dependent class III HDAC or the Sirtuin family, although the role of SIRT1 in cardiac hypertrophy is under debate [7,8], SIRT3, SIRT6 and SIRT7 are revealed to be anti-hypertrophic factors [9–11]. The HATs have five families, among which, p300 and PCAF of the GNAT family are reported to be pro-hypertrophic factors [12,13]. However, the role of other HATs in hypertrophic cardiopathy still remains elusive.

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Males absent on the first (MOF) is a member of the MYST (MOS, KB2/Sas3, Sas2 and TIP60) family of histone acetyltransferase (HAT), and it was first described in *Drosophila melanogaster* as an essential component of the X-chromosome dosage compensation of male-specific lethal (MSL) complex [14,15]. MOF is conserved among higher eukaryotes. H4K16 acetylation in higher eukaryotes is mainly carried out by MOF [16]. The function of MOF in dosage compensation is mediated by its acetyltransferase activity, which is tightly regulated by the MSL protein [15,17]. Compared to the functions in *Drosophila* dosage compensation, the roles of MOF in mammals are less well characterized. Here in this study, we found that expression level of MOF decreased in human failing and murine hypertrophic hearts. Moreover, overexpression of MOF in mouse hearts blunted cardiac hypertrophy by targeting ROS and its downstream c-Raf-MEK-ERK pathway that facilitates hypertrophy.

2. Materials and methods

2.1. Human heart samples

Four human failing heart samples were obtained from the Yantaishan Hospital Cardiac Transplant Program. Failing heart specimens were obtained from diseased hearts that were removed during orthotropic heart transplantation. Two control non-failing heart samples were obtained intraoperatively from hearts undergoing ventricular corrective surgery or from donor dysfunctional hearts. The written form of informed consent was obtained from all patients participating in this study. All procedures involving human tissue use were approved by the Yantaishan Hospital.

2.2. Animals

To generate transgenic mice with cardiac-restricted expression of human MOF (hMOF), we used a cDNA amplified from a plasmid encoding hMOF (Addgene, plasmid 25180), which was sub-cloned into the α-MHC promoter vector. Cardiac-specific hMOF transgenic mice were generated in the FVB mouse strain according to the standard procedure of the Yantaishan Hospital Transgenic facility. At 3 weeks of age, tail DNA was analyzed by genotyping with primers: Forward, 5′-TCGGAGAAACGTACCTGTGC-3′; Reverse, 5′-CCGGTTCTTGTCTACCCAC-3′. After two injections, three (founders) out of eight pups were proved to be positive. The cardiac-specific hMOF transgenic mice were backcrossed to C57/BL6 mice for six generation to obtain transgenic mice in the C57BL/6 background. All animal experiments were performed using 10∼12 weeks old male C57BL/6 mice. Non-transgenic littermates were used as controls. All animal experiments were performed with protocols approved by the Committee for the Use and Care of Experimental Animals of the Yantaishan Hospital.

2.3. Induction of hypertrophy in mice

Chronic infusion of isoproterenol (ISO, 8.7 mg/kg/d) or and angiotensin II (Ang II, 3 mg/kg/d) by implanting osmotic mini-pumps (ALZET, model 2004) into the peritoneal cavity of mice for 4 weeks was used to induce cardiac hypertrophy as described in previous publication [9]. Pressure overload hypertrophy was induced by transverse aortic constriction (TAC) of the ascending aorta of mice for 4 weeks, as described elsewhere [18].

2.4. Echocardiography of mice

Transthoracic echocardiography in mice was performed as described previously before the mice were sacrificed [9].

2.5. Histological analysis

Hearts from mice undergoing TAC or Sham surgery were excised, washed with saline solution, and placed in 10% formalin. Hearts were cut close to the apex to visualize the left and right ventricles. Several sections of hearts were prepared and stained with H&E for histopathology and then visualized by light microscopy. 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).

2.6. DHE staining

Intracellular ROS production was detected by the use of fluorescent probe dye, dihydroethidium (DHE) (Invitrogen). Briefly, frozen tissue sections (7 μM) were incubated with 10 μM DHE at 37 °C for 30 min according to the manufacturer's instructions. Red fluorescence was assessed by confocal laser scanning microscopy. ROS production was expressed as mean fluorescence intensity, which was calculated by the use of Cell Quest software.

2.7. RNA extraction and quantitative real-time PCR (q-PCR)

Total RNA from fresh human, or murine heart samples, was extracted with TRIzol (Invitrogen) and cDNA was synthesized using 2 μg RNA with the Advantage RT-for-PCR kit (BD Biosciences). We quantified relative mRNA level with q-PCR amplifications using SYBR Green PCR Master Mix (TaKaRa). The q-PCR primers used in this study are listed in Supplementary Table 1.

2.8. Western blotting

Human and murine cardiac tissues were lysed with RIPA lysis buffer supplied with mixture of protease inhibitors (Thermo). 40 μg total proteins were applied to 12% SDS–polyacrylamide gel. After electrophoresis, the proteins were transferred to PVDF membranes, which were then blocked with 5% fat-free milk for 2 h. The membranes were then probed with primary antibody for MOF (Abcam, ab71209), p-c-Raf, c-Raf (CST, 9422), p-MEK(CST, 2238), MEK, p-ERK(CST, 4094), ERK(CST, 4695) or GAPDH (Abcam, ab37168) at 4 °C overnight, and then the membranes were washed and incubated with HRP-conjugated secondary antibodies (Zhongsanjinqiao) for 2 h and finally visualized using Chemiluminescent ECL reagent (Beyotime).

2.9. Statistical analysis

All values were expressed as the mean ± SEM. Statistical differences among groups were determined using either Student's *t* test or one-way ANOVA using Graph-Pad Prism Software 6. *P* values of less than 0.05 were considered statistically significant.

3. Results

3.1. MOF is down-regulated in human failing hearts and murine hypertrophic hearts

To profile the role of MOF in heart failure and hypertrophy, we firstly assessed the expression pattern of MOF in human failing hearts. Four failing and two non-failing heart samples were used in this study. The protein and mRNA were extracted and subjected to Western blotting and q-PCR analysis respectively. The results showed that MOF expression was significantly down-regulated in failing heart samples at both protein and mRNA levels compared to those from the non-failing ones (Fig. 1A). To verify whether this

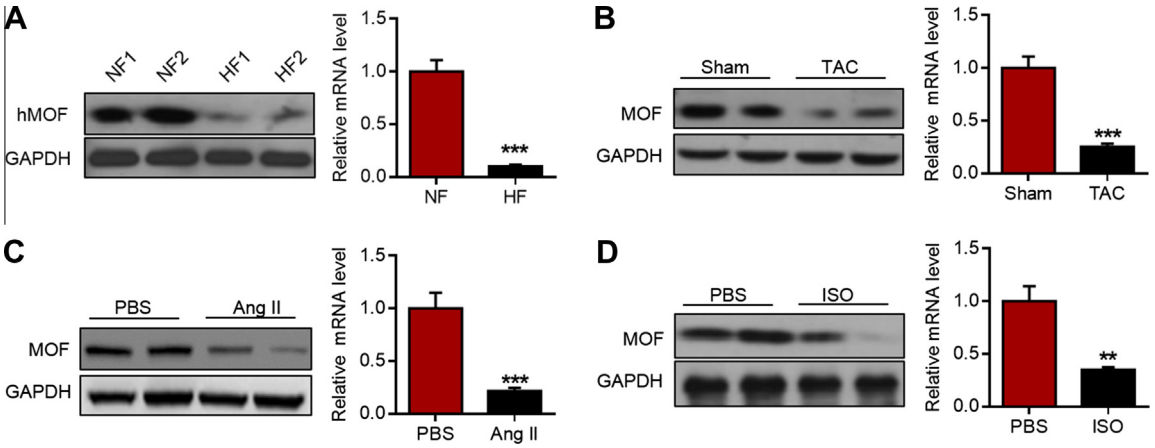

Fig. 1. MOF expression decreases in human failing hearts and murine hypertrophic hearts. (A) MOF protein and mRNA levels decrease in human failing hearts. Non-failing (NF) or failing (HF) hearts from patients were obtained and protein and RNA were extracted and subjected to Western blotting and q-PCR analysis respectively. Two non-failing and four failing human heart samples were involved in this study. $^{**}p < 0.01$ *vs.* NF. (B–D) MOF protein and mRNA levels decrease in murine hearts with hypertrophy. 10–12 weeks old male wide-type C57/LB6 mice were subjected to TAC surgery (B) or chronic infusion with Ang II (C) or ISO (D) for 4 weeks. Protein and RNA were extracted from mouse hearts, followed by Western blotting or q-PCR analysis respectively. $n = 5$ in each group of q-PCR analysis. $^{**}p < 0.01$ and $^{***}p < 0.0001$ *vs.* Sham or PBS treatment.

change occurs in murine failing hearts, we assessed the MOF expression level in mice with hypertrophy, which is one of the major features of heart failure. As the results showed, in the heart samples of TAC-induced hypertrophy, the protein and mRNA levels of MOF were significantly down-regulated (Fig. 1B). Similar results were found in the hearts from mice infused with Ang II and ISO (Fig. 1C and D). Taken together, MOF expression was reduced in human failing and murine hypertrophic hearts, indicating the involvement of MOF in hypertrophy and subsequent heart failure.

3.2. Generation of hMOF transgenic mice

As we have showed the expression pattern and potential participation of MOF in cardiac hypertrophy, we next wanted to know whether MOF is critical for the development of cardiac hypertrophy in mice. To this aim, we generated cardiac-specific human MOF transgenic (hMOF-Tg) mice. The information of the hMOF-expressing vector is shown in Fig. 2A. Three lines of founder transgenic mice were obtained (Fig. 2B). The mice developed normally and no significant difference appeared among the three lines of mice. Therefore, we chose line 1 randomly for further study. The expression pattern of hMOF in different tissues indicated that the expression of human MOF was restricted to the hearts (Fig. 2C). We did not observe any difference in blood glucose, liver weight, and body weight between the transgenic mice and their non-transgenic wide type (WT) littermates in our experiments (data not shown). At baseline, hMOF transgenic mice had no noticeable cardiac abnormalities (Fig. 2D–F). In addition, no difference in expressions of hypertrophic fetal genes between WT and hMOF-Tg mice was observed (Fig. 2G).

3.3. hMOF transgene protects mice from TAC-induced cardiac hypertrophy

Although we did not observe any differences between hMOF-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 MOF on hypertrophy *in vivo*, we induced cardiac hypertrophy in WT and hMOF-Tg mice by surgically creating TAC. Non-transgenic WT mice subjected to TAC for 4 weeks developed massive cardiac hypertrophy, as evidenced by an increased ratios of heart weight (HW)/body weight (BW), lung weight (LW)/BW and HW/ tibia length (TL, Fig. 3A–C), as well as increased left ventricular wall thickness (Fig. 3D) and decreased fractional shortening (Supplementary Table 2). Those changes were paralleled with an increase in cardiomyocyte cross-sectional area (Fig. 2E–G). Interestingly, the hearts of hMOF-Tg mice did not undergo similar pathological growth after being subjected to TAC (Fig. 3A–G). hMOF-Tg mice 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 hMOF-Tg mice compared to that in non-transgenic WT mice after TAC surgery (Fig. 3H–J). Those results indicated that hMOF overexpression blunted the development of pathologic cardiac hypertrophy in mice.

3.4. MOF regulates ROS accumulation and c-Raf-MEK-ERK pathway activation

We wanted to know the mechanism by which MOF regulates the development of cardiac hypertrophy. Reactive oxygen species (ROS) production is coupled with cardiac hypertrophy and promotes hypertrophy by activating c-Raf-MEK-ERK pathway. Our results showed that MOF overexpression markedly reduced ROS induced by TAC (Fig. 4A and B). Interestingly, we found that MOF overexpression significantly increased the expression of two pivotal enzymes clearing cellular ROS, the Catalase and MnSOD in TAC-challenged mice (Fig. 4C and D). What's more, the results showed that MOF overexpression weakened the activation of the ROS downstream c-Raf-MEK-ERK pathway, which is critically important for the development of cardiac hypertrophy (Fig. 4E). Taken together, we showed that MOF overexpression reduced cellular ROS level by promoting the expression of Catalase and MnSOD and subsequently inhibited c-Raf-MEK-ERK pathway in mouse hypertrophic hearts.

4. Discussion

Here in this study, we firstly found the down-regulation of MOF in human failing and murine hypertrophic hearts. Further, we demonstrated that MOF blunted cardiac hypertrophy by targeting

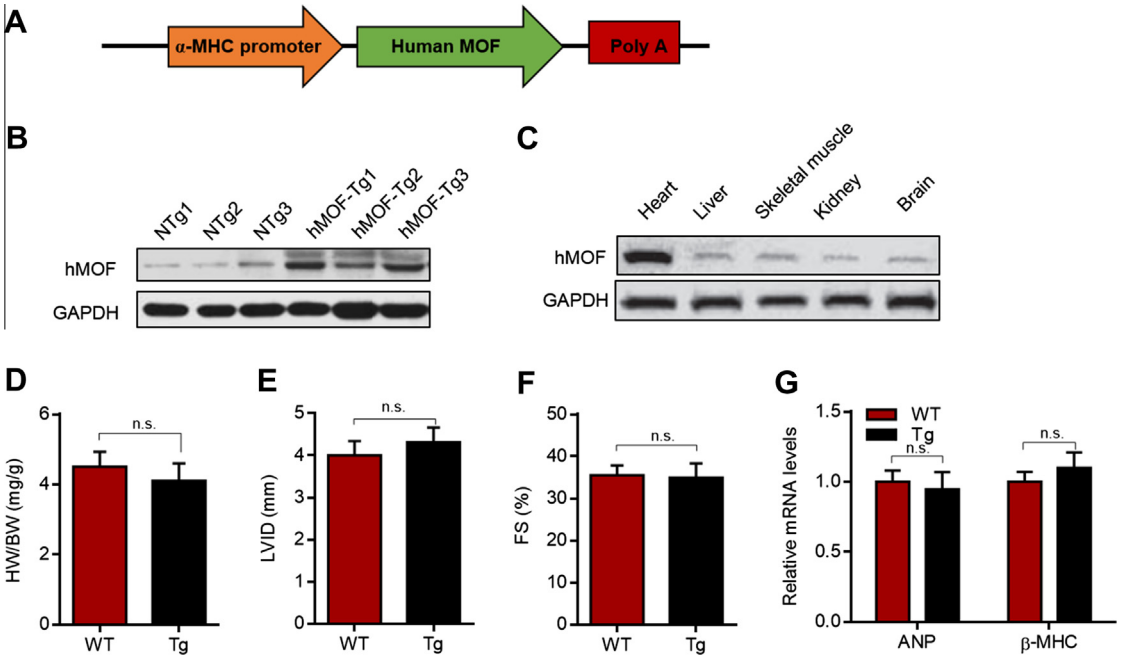

Fig. 2. Generation of cardiac-restricted hMOF transgenic (hMOF-Tg) mice. (A) A schematic of hMOF-Tg construct used to generate human MOF-Tg mouse lines. (B) Western blot analysis of hMOF expression in three wide-type (WT) and three hMOF-Tg mouse lines. (C) Western blotting analysis of the expression pattern of hMOF in heart, liver, skeletal muscle, kidney and brain from hMOF-Tg mice. (D–F) hMOF-Tg mice did not show any differences in heart function compared to that of their wide-type 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.

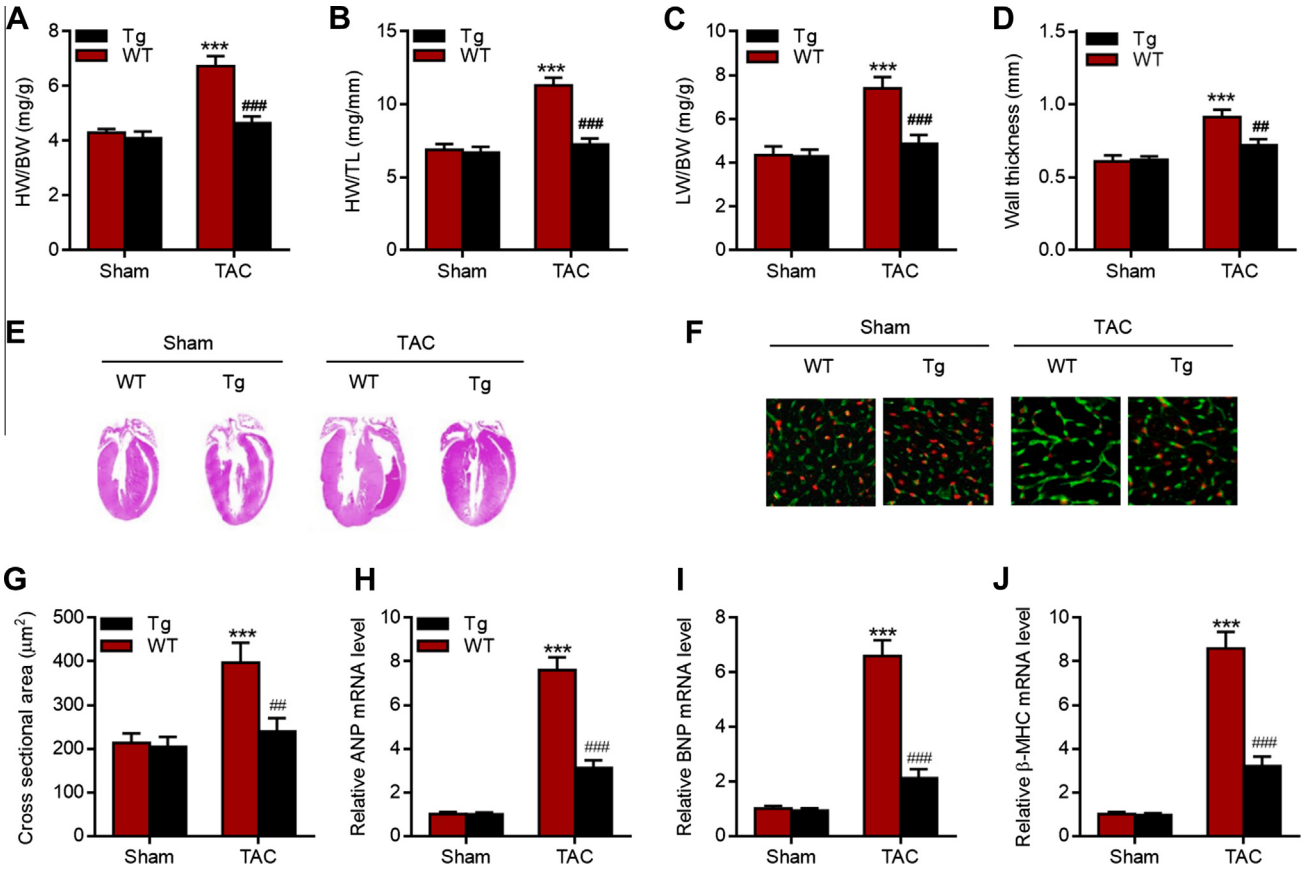

Fig. 3. hMOF overexpression blocks TAC-induced cardiac hypertrophy. Wide type (WT) non-transgenic and hMOF-Tg C57/LB6 mice of 10∼12 weeks old were subjected to Sham or TAC surgery for 4 weeks and the heart samples were analyzed. (A–C) HW/BW, HW/tibia length (TL) and lung weight (LW)/BW ratios of WT and KLF11-Tg mice undergoing control surgery (Sham) or TAC for 4 weeks. (D) Left ventricular wall thickness of WT and hMOF-Tg mice undergoing Sham or TAC surgery. (E) Heart cross-sections were stained with H&E, indicating hypertrophic growth. (F) WGA staining was performed to determine cell boundaries. (G) Quantification results of cardiomyocyte cross-sectional areas in WGA staining in (F). (H–J) mRNA levels of the indicated hypertrophic fetal genes in WT and hMOF-Tg mice underwent Sham or TAC surgery. BNP, B-type natriuretic peptide. $n = 13$ in each group. $^{***}p < 0.0001$ *vs.* WT-Sham; $^{\#\#}p < 0.001$ and $^{\#\#\#}p < 0.0001$ *vs.* WT-TAC.

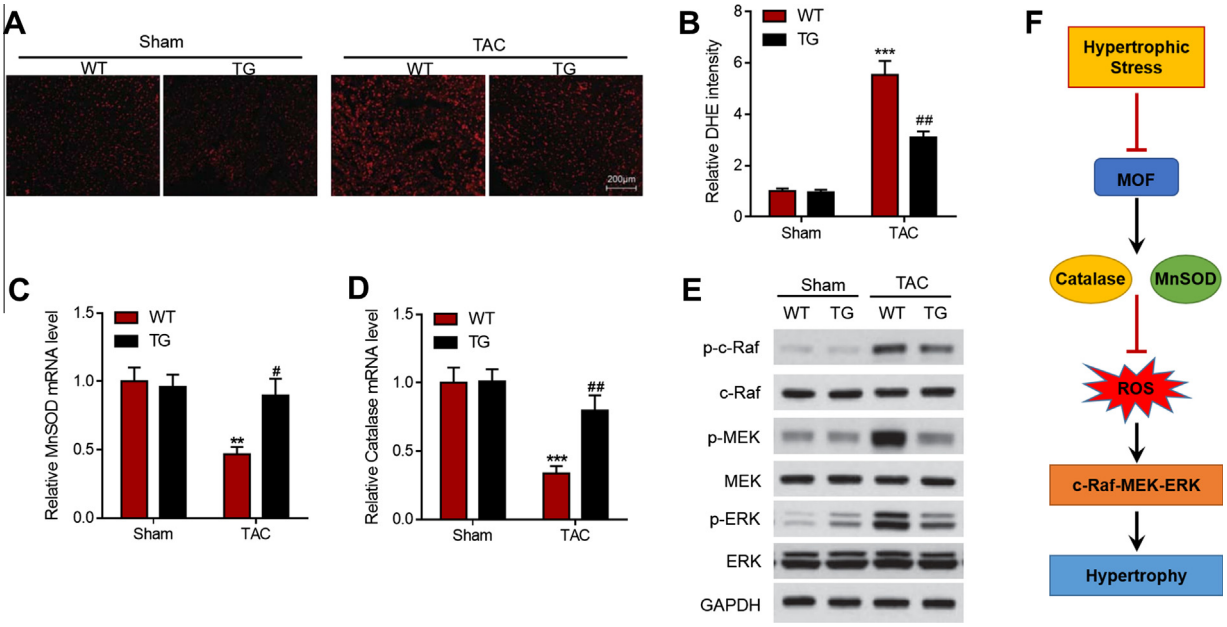

Fig. 4. MOF overexpression inhibits ROS and c-Raf-MEK-ERK pathway. (A) Representative fluorescence images of DHE staining for cellular ROS in the heart tissues of Sham or TAC challenged WT or hMOF-TG mice. (B) Quantitative analysis of the results in (A). $n = 5$ in each group. (C and D) Relative mRNA levels of MnSOD (C) and Catalase (D) in the heart tissues of Sham or TAC challenged WT-or hMOF-TG mice. $N = 5$ in each group. (E) The western blotting results showing MOF overexpression blocks TAC-induced activation of c-Raf-MEK-ERK pathway in hypertrophic heats. (D) Schematic of the participation of MOF in cardiac hypertrophy. Hypertrophic stress reduces the level of MOF, leading to the down-regulation of Catalase and MnSOD and accumulation of ROS, which results in the activation of c-Raf-MEK-ERK that promotes cardiac hypertrophy. $^{**}p < 0.01$, $^{***}p < 0.0001$ *vs.* WT + Sham; $^{\#}p < 0.05$, $^{\#\#}p < 0.001$ *vs.* WT + TAC.

ROS and its downstream c-Raf-MEK-ERK pathway using a MOF transgenic mouse model (Fig. 4F).

MOF is conserved among higher eukaryotes. In mammals, MOF is ubiquitously expressed and is clearly targeted to all chromosomes. Loss of MOF gene in mice causes peri-implantation lethality, as a result of massive disruption of chromatin architecture in a wide range of cells [19,20]. In addition, MOF is important for ATM-dependent cell-cycle checkpoint control [21], and transcription activation of Hox genes in coordination with the H3K4 methyltransferase MLL [22], by maintaining normal chromatin structure. Loss of MOF leads to severe G2/M cell cycle arrest, massive chromosome aberration, and defects in ionizing radiation-induced DNA damage repair by both non-homologous end-joining and homologous recombination [23,24]. All those effects are mediated by the acetylation activity of MOF on H4K16. However, the physiological and pathological function of MOF remains unknown. Here we identified a novel function of MOF in hypertrophic cardiopathy.

Acetylation of histones by histone acetyltransferases stimulates gene expression by relaxing chromatin structure, allowing access of transcription factors to DNA, whereas deacetylation of histones by histone deacetylases promotes chromatin condensation and transcriptional repression. Recent studies demonstrate histone acetylation/deacetylation to be a nodal point for the control of cardiac growth and gene expression in response to acute and chronic stress stimuli [25]. There are currently 18 known human HDACs, which fall into 3 classes based on their homology with 3 distinct yeast HDACs. Among them, class II HDACs have been shown to repress the growth of myocytes [6], whereas there is also increasing evidence that class I HDACs might exert opposite effects and promote cellular growth [3,26]. Mice lacking either HDAC5 or HDAC9 are viable and there is no evidence of cardiac abnormalities at early age. However, at about 6 months of age, mutant animals develop spontaneous cardiac hypertrophy that appears to reflect sensitization to age-related cardiac insults [6]. HDAC5 and HDAC9 mutant mice also develop profoundly enlarged hearts in response to pressure overload resulting from aortic constriction or constitutive cardiac activation of calcineurin, a transducer of cardiac stress signals [5,6]. HDAC2 deficiency or chemical HDAC inhibition prevents the re-expression of fetal genes and attenuates the cardiac hypertrophy in hearts exposed to hypertrophic stimuli. Resistance to hypertrophy is associated with increased expression of the gene encoding inositol polyphosphate-5-phosphatase f (Inpp5f) resulting in constitutive activation of glycogen synthase kinase 3β (GSKβ) via inactivation of thymoma viral proto-oncogene (Akt) and 3-phosphoinositide-dependent protein kinase-1 (Pdk1). In contrast, HDAC2 transgenic mice have augmented hypertrophy associated with inactivated Gsk3β. Chemical inhibition of activated Gsk3β allows HDAC2-deficient adults to become sensitive to hypertrophic stimulation [3]. The functions of NAD^+-dependent class III HDACs or the Sirtuins in hypertrophy are different from each other. The function of SIRT1 in the heart is still under debate. It seems that its negative or positive role in cardiac hypertrophy depends largely upon the individual effect factors [7,8]. The hearts of SIRT2 knockout mice, and wild-type mice treated with a specific pharmacological inhibitor of SIRT2, show marked protection from ischaemic injury [27]. Interestingly, SIRT3, SIRT6 and SIRT7 could protect hearts from hypertrophy by deacetylating Foxo3a, blocking IGF-Akt signaling or deacetylating p53 respectively [9–11]. Those findings indicate that different HDACs have different roles in hypertrophic cardiopathy, and imbalance of HDACs leads to the development of cardiac hypertrophy. Interestingly, the HDACs can influence each other in the progress of cardiac growth. The significance of interclass crosstalk in the development of cardiac hypertrophy has recently been identified. Eom et al. [13] showed that the balance of HDAC2 acetylation is regulated by PCAF and HDAC5 in the development of cardiac hypertrophy. During cardiac hypertrophy, HDAC5 is phosphorylated and is translocated to the cytoplasm, which leads to the acetylation of HDAC2 and subsequent cardiac hypertrophy. Importantly, the interaction between HDACs and HATs has also been revealed in that study.

Current studies indicate that HATs are pro-hypertrophic. Among the five families, the PCAF of the GNAT family and CREB-binding protein (CBP) p300 have been shown to block the development of pathological hypertrophy. Both p300 and PCAF successfully induce cardiac hypertrophy either by transcriptional activation of heart-specific genes or by acetylation of non-histone substrates such as GATA4 [28,29]. In addition, PCAF, but not p300, induced acetylation and following activates HDAC2 when hypertrophy occurred [13]. Here in this study, we identified MOF, another class of HAT, as an anti-hypertrophic factor. MOF is the first HAT that is identified to be a negative mediator of cardiac hypertrophy. These findings strongly indicated that HATs exhibit diverse functions in hypertrophic cardiopathy. The dynamic acetylation and deacetylation of histones play essential role in hypertrophy Imbalance of histone acetylation triggers the expression of hypertrophic fetal genes. The interaction between HDACs and HATs critically controls the modification statue of histone, and orchestrates the response to hypertrophic stimuli and the development of cardiac hypertrophy.

Conflict of interest

None.

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.2014.04.112.

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