Histone Acetyltransferase Activity of p300 Is Required for the Promotion of Left Ventricular Remodeling After Myocardial Infarction in Adult Mice In Vivo

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Background—Left ventricular (LV) remodeling after myocardial infarction is associated with hypertrophy of surviving myocytes and represents a major process that leads to heart failure. One of the intrinsic histone acetyltransferases, p300, serves as a coactivator of hypertrophy-responsive transcriptional factors such as a cardiac zinc finger protein GATA-4 and is involved in its hypertrophic stimulus-induced acetylation and DNA binding. However, the role of p300-histone acetyltransferase activity in LV remodeling after myocardial infarction in vivo is unknown.

Methods and Results—To solve this problem, we have generated transgenic mice overexpressing intact p300 or mutant p300 in the heart. As the result of its 2-amino acid substitution in the p300-histone acetyltransferase domain, this mutant lost its histone acetyltransferase activity and was unable to activate GATA-4–dependent transcription. The two kinds of transgenic mice and the wild-type mice were subjected to myocardial infarction or sham operation at the age of 12 weeks. Intact p300 transgenic mice showed significantly more progressive LV dilation and diminished systolic function after myocardial infarction than wild-type mice, whereas mutant p300 transgenic mice did not show this.

Conclusions—These findings demonstrate that cardiac overexpression of p300 promotes LV remodeling after myocardial infarction in adult mice in vivo and that histone acetyltransferase activity of p300 is required for these processes. (Circulation. 2006;113:679-690.)

Key Words: hypertrophy ▪ myocytes ▪ signal transduction

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Hypertrophic stimuli initiate a number of subcellular signaling pathways, which finally reach the nuclei of cardiac myocytes and change the pattern of gene expression.3,4 Transcription factors that mediate these changes include myocyte enhancing factor-2,5 serum response factor,6 AP-1,7 and a zinc finger protein, GATA-4.7,8 The involvement of multiple transcription factors in hypertrophic responses suggests that these factors are coordinately activated. An adenovirus E1A-associated protein, p300, acts as a coactivator of these hypertrophy-responsive transcription factors. In addition, p300 serves as an intrinsic histone acetyltransferase (HAT) and promotes an active chromatin configuration.9–11 p300 protein can also acetylate certain nonhistone proteins such as DNA-binding transcription factors.11–14 Acetylation is emerging as a posttranslational modification that is essential for the regulation of transcription and that modifies transcription factor affinity for binding sites on DNA, stability, and/or nuclear localization. Our previous study demonstrated that p300 can induce the acetylation and DNA binding of GATA-4. During myocardial cell hypertrophy, the acetylated form of GATA-4 and its DNA binding markedly increase, concomitant with an increase in p300 expression. In addition, a dominant-negative form of p300 inhibits agonist-induced

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hypertrophy, demonstrating a critical role of p300 in hypertrophic responses in cardiac myocytes in culture. However, the precise role of p300 HAT activity in LV remodeling after MI in vivo is unknown. The present study was performed to solve this problem.

**Methods**

**Plasmid Constructs**

The expression vectors pCDNA4g, pCMVβ-gal, pCMVwtp300, and pCMVHATmutp300 contain the cytomegalovirus promoter/enhancer fused to cDNA encoding murine GATA-4, β-galactosidase, a full-length human intact p300, or mutant p300, in which double amino acid substitution mutations were introduced, respectively. pCMVwtp300 and pCMVHATmutp300 were gifts from Dr Richard Eckner, University of Medicine and Dentistry of NJ. The reporter plasmid pANF-luc consists of the firefly luciferase (luc) cDNA driven by a 131-bp rat atrial natriuretic factor (ANF) promoter sequence. pET-1CAT contains the transcription start site-proximal 204 bp of the wild-type (WT) rat endothelin-1 (ET-1) promoter fused to a bacterial chloramphenicol acetyltransferase (CAT) gene. pRSVCAT and pRSVluc contain a bacterial CAT and a firefly luc gene, respectively, driven by Rous sarcoma virus (RSV) long terminal repeat sequences.

**Analysis of the Acetylation State of GATA-4 and Western Blotting**

Cell culture of COS7 cells, immunoprecipitation, and Western blotting for acetylated lysine and GATA-4 were performed as previously described. We used goat anti-GATA-4 polyclonal antibody (Santa Cruz Biotechnology) for immunoprecipitation, and rabbit polyclonal antibody against acetylated lysine (Cell Signaling) and mouse anti–GATA-4 monoclonal antibody (Santa Cruz Biotechnology). Mouse anti-p300 monoclonal antibody (Upstate Biotechnology), mouse anti–β-actin monoclonal antibody (Sigma), and mouse anti-GAPDH monoclonal antibody (Molecular Probes) were used for Western blotting. The level of acetylated GATA-4 was also analyzed by pulse-labeling as previously described.

**Electrophoretic Mobility Shift Assays**

Electrophoretic mobility shift assays (EMSA), with the GATA-4 site in the rat ET-1 promoter used as a probe, were carried out as previously described. We also used a double-stranded oligonucleotide containing the Sp-1 binding site as a control probe (Santa Cruz Biotechnology).

**Transfection and Luciferase/CAT Assays**

COS7 cells were transfected with the indicated amounts of plasmid DNA through the use of LIPOFECTAMINE (Life Technologies, Biotechnology). The reporter plasmid pANF-luc consists of the endothelin-1 (ET-1) promoter fused to a bacterial chloramphenicol acetyltransferase (CAT) gene. pRSVCAT and pRSVluc contain a bacterial CAT and a firefly luc gene, respectively, driven by Rous sarcoma virus (RSV) long terminal repeat sequences.

**Western Blotting**

Western blotting for acetylated lysine and GATA-4 were performed as previously described. Western blotting in COS7 cells transfected with pcDNA-GATA4 in the presence or absence of pCMVwtp300 or pCMVHATmutp300, an expression plasmid encoding mutant p300 (HATmut p300). No protein was immunoprecipitated with control IgG (Figure 1A, lane 4). Forced expression of intact p300 induced acetylation of GATA-4, whereas expression of HATmut p300 did not induce acetylation (Figure 1A, lane 4). Forced expression of intact p300 induced acetylation of GATA-4, whereas expression of HAT-mut p300 did not induce acetylation (Figure 1A, upper panel). GATA-4 was similarly immunoprecipitated with anti-GATA-4 antibody in the 3 groups (Figure 1A, lower panel). Before immunoprecipitation, the expression levels of GATA-4 were similar in the 3 groups (Figure 1B, middle panel). Furthermore, intact p300 and HATmut p300 were expressed at similar levels (Figure 1B, upper panel). We also performed pulse-labeling experiments. Incorporation of sodium [14C]acetate into GATA-4 protein was clearly detected in pCMVwtp300-transfected cells but not in pCMVHATmutp300-
transfected ones (Figure 1C). Next, the same extracts used in the experiments shown in Figure 1, A and B, were subjected to EMSAs by using the GATA-4 site of ET-1 promoter as a probe (Figure 1D). Competition and supershift experiments demonstrated that the retarded band (indicated by an arrow) represents an interaction of the probe with GATA-4. Notably, expression of intact p300 markedly increased GATA-4/DNA binding (lane 2) compared with pCMVβ-gal expression (lane 1), whereas that of mutant p300 only modestly increased (lane 3, Figure 1, D and F). Sp-1/DNA binding was similar among the 3 groups (Figure 1E). These findings demonstrate that the HAT activity of p300 plays a critical role in acetylation and DNA binding of GATA-4.

HAT Activity of p300 Is Required for Synergistic Activation of GATA-4–Dependent Promoters

To examine whether the HAT activity of p300 participates in GATA-4–dependent transcription of the ET-1 and ANF genes, we performed transient transfection experiments. As shown in Figure 2, A and B, transfection of either pcDNA4 (lane 2), pCMVwtp300 (lane 3), or pCMVHATmutp300 (lane 5) alone resulted in only modest increases in ANF and ET-1 promoter activities. Transfection of pCMVwtp300 in addition to pGATA-4 (lane 4) induced a marked activation of these promoter activities. However, transfection of pCMVHATmutp300 only modestly augmented GATA-4–dependent ET-1 or ANF transcription (lane 6). Intact p300 and HATmutant p300 were similarly expressed in extracts from pCMVwtp300-transfected and pCMVHATmutp300-transfected cells (Figure 2C, upper panel, lanes 3 to 6). GATA-4 levels were also similar among lanes 2, 4, and 6 (Figure 2C, middle panel). These findings demonstrate that p300 and GATA-4 synergistically activate the ANF and ET-1 promoters and that the HAT activity of p300 is required for these activations.

HAT Activity of p300 Is Required for Acetylation of GATA-4 in the Mouse Heart

To further investigate the role of p300 HAT activity in LV remodeling after MI in vivo, we generated Tg mice

Figure 1. Histone acetyltransferase (HAT) activity of p300 is required for acetylation and DNA binding of GATA-4. A, COS7 cells were transfected with 2 μg of pcDNA4 in the presence or the absence of pCMVβ-gal in the presence or the absence of pCMVβ-gal (10 μg) or pCMVmutp300 (10 μg), as indicated. The total amount of DNA was kept constant by cotransfecting pCMVβ-gal. Protein extracts from these cells were immunoprecipitated with goat anti-GATA-4 polyclonal antibody, followed by sequential Western blotting with rabbit antiacetylated lysine polyclonal antibody and with rabbit anti–GATA-4 polyclonal antibody. B, The extracts used in A before immunoprecipitation were subjected to Western blotting with the use of antibodies against p300, GATA-4, and β-actin. C, COS7 cells were transfected with 2 μg of pcDNA4 in addition to 10 μg of pCMVwtp300 or pCMVmutp300 and were pulse-labeled with [3H] thymidine for 3 hours. The protein extracts were immunoprecipitated with goat anti–GATA-4 polyclonal antibody or with normal goat IgG and resolved by SDS-PAGE. D and E, The same extracts used in A and B were probed with a radiolabeled double-stranded oligonucleotide containing the GATA-4 site in the ET-1 promoter (D) and with one containing the Sp-1 site (E). F, The amount of GATA-4/DNA binding (indicated by an arrow) was quantified by densitometry with the use of NIH image 1.61.
overexpressing intact p300 or HATmut p300 in the heart. Among multiple lines we obtained, we selected two independent lines for each type of Tg mouse (intact p300-Tg: lines 21 and 39; HATmut p300-Tg: lines 17 and 23) because the expression levels of the transgene in the heart were similar among these four lines. Since similar findings were obtained for the two lines in each kind of Tg mice, we show in the present study combined data of these two lines.

At the age of 12 weeks, cardiac function and morphology of each type of Tg mice were similar to those of the corresponding WT mice. These mice were then subjected to either sham operation or MI operation. Five weeks later, extracts from the whole LV except for the scar area of these mice were subjected to Western blotting with anti-p300 antibody that recognized the proteins produced from both transgenes (intact p300 and HATmut p300) as well as endogenous p300 (Figure 3A, upper panel, and Figure 3B). In the sham operation groups, intact p300- and HATmut p300-Tg mouse hearts showed an 8-fold increase in total p300 content, compared with their corresponding WT mouse hearts (compare lanes 1 and 3 and lanes 5 and 7 in Figure 3B). Endogenous p300 levels in WT mouse hearts increased after MI (compare lanes 1 and 2 and lanes 5 and 6 in Figure 3B). However, in the hearts of intact p300-Tg and HATmut p300-Tg mice, total p300 levels were similar between the sham operation and MI groups (compare lanes 3 and 4 and lanes 7 and 8 in Figure 3B). On the other hand, the total amounts of cardiac GATA-4 were similar in all groups (Figure 3A, middle panel).

Next, we investigated the role of p300 HAT activity in GATA-4 acetylation in mouse hearts. Signals of acetylated GATA-4 (Figure 3C, upper panel) were distinct in intact p300-Tg mice (lanes 3 and 4) but undetectable or very weak in WT mice (lanes 1 and 2) and HATmut p300-Tg mice (lanes 5 and 6). In all kinds of mice, the signals were higher in the MI groups than in the sham-operated groups. GATA-4 was similarly immunoprecipitated with anti–GATA-4 antibody in all these groups (Figure 3C, lower panels, lanes 1 to 6). No protein was immunoprecipitated with control IgG (lanes 7 and 8). These findings demonstrate that the overexpression of p300 in the heart promotes the acetylation of GATA-4 and that the HAT activity of p300 is required for this effect.

Cardiac Overexpression of Intact p300 but Not of Mutant p300 Augments LV Remodeling After MI

All sham-operated mice survived throughout the study. We next examined the mortality of MI-operated mice after the operation. Mortality at day 0, which indicates acute surgical death due to MI, did not differ among WT, intact p300-Tg, and HATmut p300-Tg mice (Figure 4A). The 5-week survival rate was significantly lower in intact p300-Tg mice than the corresponding WT mice but was similar between HATmut p300-Tg and WT mice. Autopsy revealed considerable pleural effusion and pulmonary congestion in almost all of the mice that died later than 2 days after MI, suggesting that these mice predominantly died of heart failure. Compared with HATmut p300-Tg mice, the mortality rate of intact p300-Tg mice was remarkably increased later than 2 days after MI. Thus, this increase may come from increased incidence of heart failure in intact p300-Tg mice after MI.

Next, we performed physiological study to evaluate cardiac morphological and functional changes at 5 weeks.
after sham or MI operation. Echocardiographic data in the sham-operation groups was similar among all kinds of mice (WT, intact p300-Tg, and HATmut p300-Tg). After MI, however, increase in LV end-diastolic and end-systolic dimension and decrease in percent fractional shortening were more prominent in intact p300-Tg than their corresponding WT mice but were similar between HATmut p300-Tg and their WT mice. In summary, diastolic function is impaired in intact p300-Tg mice compared with other kinds of mice. In addition, in accord with the data obtained by echocardiography, MI-induced changes, consisting of decreased contractility, chamber dilation, and low output, were more prominent in intact p300-Tg mice than in HATmut p300-Tg or WT mice.

Consistent with the findings of the physiological analysis, histological analysis at 5 weeks after MI revealed a severely dilated LV cavity with a thin infarct wall in intact p300-Tg mice compared with HATmut p300-Tg or WT mice (Figure 6A). The absolute infarct size was similar among the different kinds of mice, whereas the noninfarct area was modestly increased in intact p300-Tg mice (Figure 6B). There was no significant difference in percentages of infarct area relative to total LV area among WT (23.4%), intact p300-Tg (21.3%), and HATmut p300-Tg (22.1%) mice, suggesting that severe LV remodeling in intact p300-Tg mice developed independent of infarct size in these mice. In addition, in the MI groups, LV cavity area (Figure 6C) and heart weight/body weight ratio (Figure 6D) after MI were larger in intact p300-Tg than HATmut p300-Tg or WT mice.

Although there were no significant differences in histology among the different kinds of sham-operated mice, cross-sectional myocardial cell diameter at 5 weeks after MI was larger in intact p300-Tg mice than in WT or HATmut p300-Tg mice (Figure 7, A and B). In the MI groups, the population of noncardiomyocytes in the infarct area (Figure 7C) and the amount of fibrosis in the infarct area (Figure 7D) and in the noninfarcted LV walls (Figure 7E) were similar among WT, intact p300-Tg, and HATmut p300-Tg mice. These findings demonstrate that p300 promotes MI-induced LV remodeling associated with the hypertrophy of individual myocytes and that the HAT activity of p300 is required for this promotion.

HAT Activity of Cardiac p300 Is Involved in Increase in GATA-4/DNA binding and LV ET-1 Expression After MI

To examine changes in GATA-4/DNA-binding after MI in WT, intact p300-Tg, and HATmut p300-Tg mouse hearts, EMSAs using the ET-1 GATA site as a probe were performed in cardiac nuclear extracts from these mice 5 weeks after the operation. Competition and supershift experiments demonstrated that the retarded band (indicated by an arrow) represents an interaction of the probe with cardiac GATA-4.
GATA-4/DNA binding in the heart was increased after MI in each kind of mouse. In the MI groups, however, the intensity of GATA-4/DNA binding was significantly higher in intact p300-Tg than in WT mice but was similar between HATmut p300-Tg and WT mice (Figure 8, B and C). In contrast, cardiac Sp-1 binding activities were similar among all kinds of mice (Figure 8D). Finally, we measured LV levels of ET-1, a downstream target of the

Figure 4. Survival rates and echocardiography data after MI. At the age of 12 weeks, intact p300-Tg mice, their corresponding WT mice, HATmut p300-Tg mice, and their corresponding WT mice were subjected to sham or MI operation. A, Kaplan-Meier survival curves of MI-operated mice. B, Echocardiographic data at 5 weeks after sham or MI operation. HR indicates heart rate; BP, blood pressure; LVEDD, left ventricular chamber diameter in end-diastole; LVESD, left ventricular chamber diameter in end-systole; FS, fractional shortening. C, Representative photographs of M-mode images.
**Figure 5.** Hemodynamics of Tg and WT mouse hearts after MI. Five weeks after sham or MI operation, hemodynamics of Tg mice and their WT mice were examined as described in the Methods section. A, Values represent mean ± SEM of 3 to 7 mice in each group, as indicated. ESP indicates end-systolic pressure; EDP, end-diastolic pressure; ESV, end-systolic volume; EDV, end-diastolic volume; SI, stroke volume index; CI, cardiac index; dP/dtmax, maximum derivative of change in systolic pressure over time; dP/dtmin, minimum derivative of change in diastolic pressure over time; r, time constant of isovolumic relaxation; NL Ees, normalized end-systolic volume elastance; NL Eed, normalized end-diastolic volume elastance; PRSW, preload recruitable volume work. B, Representative curves of pressure-volume relations, LV pressure, and slope of derivative of change in systolic pressure over time (dP/dt) in sham versus MI.
p300/GATA-4 pathway (Figure 8E). Although LV ET-1 levels in the sham operation groups did not differ among WT, intact p300-, and HATmut p300-Tg mice, the levels were increased after MI in each kind of mouse. Consistent with the findings of EMSAs, the LV ET-1 levels in the MI groups were higher in intact p300-Tg than HATmut p300-Tg mice. These findings suggest that the HAT activity of p300 is involved in the MI-induced increase in the LV ET-1 level as well as GATA-4/DNA binding.

**Discussion**

The present study investigated the role of p300 HAT activity in LV remodeling after MI in vivo. The HAT domain of p300 has been mapped previously to residues 1284 to 1669. 18 p300 HAT activity is able to acetylate not only histone tails but also transcriptional regulators such as p53 or p300 itself. 11–14 HATmut p300, a mutant we used in the present study, was almost completely defective in histone-p53 acetylation and autoacetylation. 18 In agreement with these findings, HATmut p300 was unable to induce acetylation or DNA binding of GATA-4 in adult mouse hearts as well as in vitro, although acetylation of other components of the transcriptional machinery might be affected in the heart of HATmut p300-Tg. However, HATmut p300 did not act as a transcriptional repressor but had modest ability to enhance GATA-4–dependent transcription. These findings suggest that HATmut p300 acts as a silent mutant and not as a dominant-negative mutant. Three cysteine-histidine–rich domains, which are important in mediating protein-protein interaction, are conserved in HATmut p300. Therefore, the bridging function of HATmut p300 will be conserved in this mutant and might be involved in the modest activation of GATA-4–dependent transcription.

The present study demonstrated that acetylation of GATA-4 in WT hearts increased after MI, concomitant with an increase in expression of endogenous p300. Thus, p300 may be one of the factors that mediate the acetylation during LV remodeling. However, acetylation and DNA binding of GATA-4 in Tg mouse hearts increased after MI even without an increase in the total p300 content. During myocardial cell hypertrophy, activation of mitogen-activated protein kinases induces p300 phosphorylation, which results in enhanced p300 HAT activity. 23,24 Thus, such modification of p300 as well as changes of its quantity might regulate the acetylation of GATA-4 during LV remodeling after MI. It is also possible that other HATs...
such as p300/CBP associating factor (P/CAF) play a role in MI-induced acetylation. In addition, acetylation of nuclear proteins is regulated by histone deacetylases. Therefore, to clarify the precise mechanisms of acetylation during LV remodeling after MI, it would be interesting to examine the association of GATA-4 or myocyte enhancing factor-2 with p300 and histone deacetylases during this process.

In the absence of MI, activation of p300 alone in female mice does not lead to increase in heart size or increased mortality rates at the age of 17 weeks or younger. However, LV remodeling after MI was more exaggerated in intact p300-Tg mice than in HATmut p300-Tg mice. In close association with LV remodeling, acetylation and DNA binding of GATA-4 in the MI group were higher in intact p300-Tg mice than in HATmut p300-Tg mice. The LV level of ET-1, a downstream target of GATA-4, revealed a similar tendency to its DNA binding. These findings demonstrate that a sufficient level of p300 HAT activity is critical for the acetylation and DNA binding of GATA-4 and for promotion of LV remodeling after MI in adult mice in vivo. Interestingly, despite the overexpression of p300, interstitial cell proliferation and fibrosis

**Figure 7.** Histological analysis of Tg and WT mouse hearts after MI. A through E, Five weeks after sham or MI operation, histological sections of mouse hearts were subjected to hematoxylin and eosin staining (A through C) or sirius red staining (D and E). A, Representative photographs at magnification ×400. B, The average of 50 individual myocardial cell diameters were calculated for 1 animal, and results from 5 animals in each group are expressed as mean ± SD. C, Cell density in infarcted area was measured in each group. D and E, Percentage of areas taken up by collagen fibers in either infarcted (D) or noninfarcted (E) region. Results from 7 animals in each group are expressed as mean ± SD (C through E).
Figure 8. GATA-4/DNA binding and endothelin-1 (ET-1) level after MI in Tg and WT mouse hearts. A, Five weeks after sham or MI operation, 10 μg of protein extracts from mouse hearts were probed with a radiolabeled double-stranded oligonucleotide containing the GATA site in the ET-1 promoter. Unlabeled competitor DNAs were present at a 100-fold molar excess where indicated: lane 2, a wild-type GATA oligonucleotide (WT-GATA); lane 3, a mutant GATA oligonucleotide (Mut-GATA). Supershift assays were performed in the presence of 4 μg of control IgG, anti–GATA-4 antibody, or anti–GATA-6 antibody, as indicated (lanes 4 to 6). B and C, The amount of GATA-4/DNA binding (indicated by an arrow) was compared among extracts from each group. Representative photograph (B) and quantitative data (C) are shown. The relative amount of DNA binding in the hearts of sham-operated WT mice was set at 1.0. Values are mean ± SD of 6 animals in each group. D, The same extracts used for (B) and (C) were also probed with radiolabeled double-stranded oligonucleotide containing the Sp-1 site. E, Results of LV ET-1 levels from more than 10 animals in each group are expressed as mean ± SD.
remain unaffected, whereas interstitial cell proliferation is an important feature of LV remodeling. However, individual myocyte growth was remarkable in intact p300-Tg mouse hearts compared with WT mouse hearts. This observation suggests that p300 augments post-MI remodeling by affecting growth of each myocyte.

Recent studies suggest that GATA-6 as well as GATA-4 is involved in the hypertrophic response in cardiac myocytes. By supershift experiments, the present study demonstrated that GATA-6 is not a major GATA factor contained in cardiac nuclear complex formed with ET-1 GATA site (Figure 8A). However, these data do not rule out the possible redundant and compensative roles of GATA-6 during LV remodeling after MI. In addition, p300 is able to interact not only with GATA-4, but also with other hypertrophy-responsive transcription factors such as myocyte enhancing factor-2, nuclear factor of activated T-lymphocyte, and AP-1. Our findings might be applicable to these factors as well. The present study suggests that HAT activity of p300 could be a pharmacological target for LV remodeling after MI in humans. Recently, a natural compound, anacardic acid, was shown to inhibit HAT activity. Therefore, it would be interesting to test whether p300 HAT inhibitors can block MI-induced LV remodeling in vivo.

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Disclosures
None.

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Left ventricular remodeling after MI consists of dynamic and biological changes of the heart. During LV remodeling, hypertrophy of each surviving myocyte occurs in proportion to infarct size and represents a major process that leads to heart failure. Hypertrophic stimuli initiate a number of subcellular signaling pathways, which finally reach the nuclei of cardiac myocytes and change the pattern of gene expression. To establish an efficient pharmacological therapy for LV remodeling, it is critical to identify a common nuclear target of hypertrophic stimuli in cardiac myocytes. One of the intrinsic histone acetyltransferases, p300, serves as a coactivator of hypertrophy-responsive transcriptional factors such as a cardiac zinc finger protein GATA-4 and is involved in its hypertrophic stimulus-induced acetylation and DNA binding. The present study demonstrates that cardiac p300 augments post-MI remodeling by affecting growth of each myocyte in adult mice in vivo. In addition, a sufficient level of p300 HAT activity was required for the acetylation and DNA binding of GATA-4 and for the promotion of LV remodeling after MI. These data suggest that HAT activity of p300 could be a pharmacological target for LV remodeling after MI in humans.
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