Journal of Cellular Biochemistry 94:566–572 (2005)

Histone Acetyltransferase Activity of p300 Enhances the Activation of IL-18 Promoter

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Abstract Interleukin-18 (IL-18), an important regulator of innate and acquired immune responses expressed from a variety of cell types, is a pleiotropic cytokine in the development of T helper type 1 (Thl) cells. The p300/CBP (CREB-binding protein) coactivator proteins are important histone acetyltransferases (HATs) that regulate the transcription of many genes. Whether p300/CBP play a role in the IL-18 expression has not been investigated previously. In this study, we analyzed the roles of p300 in the regulation of mouse IL-18 by using RT-PCR and a series of co-transfection studies. We showed that p300 had a stimulating effect on the endogenous IL-18 mRNA synthesis and on the activity of IL-18 p1 promoter. The results also showed that IL-18 p1 promoter activity was enhanced by p300 in a dose-dependent manner. Moreover, the p300-mediated activation function can be suppressed by the adenovirus E1A protein, which inhibits the HAT function of p300. Also, a mutation in p300 HAT region abolished the effect of p300 on IL-18 activation. These data further indicate that the acetylase activity of p300 was indispensable to its function. Furthermore, we found that p300 was able to enhance the effect of the transcription factor c-Fos on activation of the IL-18 promoter. Data presented in this paper implicate important roles of p300 in the transcriptional regulation of IL-18. J. Cell. Biochem. 94: 566–572, 2005.

Key words: histone acetyltransferase; interleukin-18; p300; c-Fos

Interleukin-18 (IL-18), also known as interferon-gamma inducing factor (IGIF), is a pleiotropic cytokine playing important roles in the development of T helper type 1 (Thl) cells, which are required for cell-mediated immune responses [Okamura et al., 1995; Dinarello et al., 1998; Gracie et al., 2003]. IL-18 is produced by activated blood monocytes and tissue macrophages such as Kupffer cells, eritoneal cells, epidermal kerainocytes, and osteoblastic cells. It acts primarily as a co-stimulant for Th1 cells, inducing production of IFN-γ, IL-2 and GM-CSF, stimulating IL-2R α-chain expression, and Th1 cell proliferation [Nakanishi et al., 2001]. As a recently described member of the IL-1 cytokine superfamily, IL-18 is now recognized as an important regulator of innate and acquired immune responses.

The regulation of IL-18 gene expression has been studied in some details. It was reported that mouse IL-18 gene expression was controlled by the activities of two promoters (p1 promoter and p2 promoter) lacking the TATA box and GC-rich region [Kim et al., 2000]. It was also demonstrated that the upstream promoter (p1 promoter) was inducible by lipopolysaccharides (LPS) [Tone et al., 1997]. Its activity was upregulated in activated macrophage and T cell lines. The downstream promoter (p2 promoter) had the constitutive activity. There were two transcription factors interacting with the cis-acting elements that are reported to control the activity of the upstream promoter [Kim et al., 2000]. One is the interferon (IFN) consensus sequence-binding protein (ICSBP). Mutagenesis studies indicated that the ICSBP binding site between −39 and −22 was critical for the

Abbreviations used: CBP, CREB-binding protein; HAT, histone acetyltransferase; IL, interleukin; LPS, lipopolysaccharide; PCR, polymerase chain reaction.

Haijing Sun and Jun Lu contributed equally to this work.

Grant sponsor: National Science Foundation of China; Grant number: 30370316; Grant sponsor: Major State Basic Research Project of China; Grant number: G1999053902.

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Received 3 March 2004; Accepted 30 April 2004

DOI 10.1002/jcb.20194

induction of IFN-gamma. Another element, an AP-1 site between −1,120 and −1,083, was also important. Electrophoresis mobility shift assay (EMSA) using an AP-1-specific oligonucleotide demonstrated that either IFN-gamma or LPS treatment stimulated the AP-1-binding activity. In this study, our interest in the transcriptional regulation of IL-18 has been focused on the activity of p1 promoter since it is inducible.

The p300 and CBP proteins are important histone acetyltransferases (HATs) [Chan et al., 2001], which modify chromatin by acetylating lysine residues within the N-terminal tails of core histones to promote destabilization of histone-DNA interactions in nucleosomes resulting in an increased accessibility of the chromatin template to the transcriptional machinery [Roth et al., 2001]. Both p300 and CBP have been implicated in the regulation of gene expression, including IL-2, IL-4, IL-6, IL-8, IL-13, IL-16 [Avots et al., 1999; Bannert et al., 1999; Vanden Berghe et al., 1999; Sisk et al., 2000; Huang and McCance, 2002; Yamashita et al., 2002]. The actions of p300 involve acetylation of core histones leading to changes in chromatin structure [Kouzarides, 2000], as well as direct acetylation of transcription factors [Marzio et al., 2000; Kawai et al., 2001]. Besides their acetyltransferase activities, p300 and CBP function in part by mediating the assembly of multi-protein complexes serving as molecular scaffolds or bridges [Chan et al., 2001]. Both p300 and CBP possess intrinsic acetyltransferase activities that are required for their function as coactivators [Ogryzko et al., 1996]. p300 and CBP have been implicated in actions of a large number of transcription factors, based on experiments using neutralizing antibodies against p300/CBP, in vivo gene deletion, and specific ribozymes [Chakravarti et al., 1996; Kamei et al., 1996; Torchia et al., 1997; Kurokawa et al., 1998]. Acetylation of these proteins can either increase DNA binding [Dai and Markham, 2001; Erickson et al., 2001] or decrease DNA binding [Munshi et al., 1998], as well as inhibit protein–protein interaction [Waltzer and Bienz, 1998].

Recently, Koyama et al. [2002] reported that histone deacetylerase inhibitors regulated the expression of IL-18, suggesting that HATs such as p300 may also play a role in the activation of IL-18. To investigate whether p300 is involved in the activation of IL-18 by LPS, we performed RT-PCR and a series of co-transfection studies in 293T cell. Our results revealed that p300 had an enhancing effect on the expression of endogenous IL-18 mRNA and on the activity of the IL-18 p1 promoter. We also demonstrated that the acetylase activity of p300 was indispensable for the enhancement of promoter activity. The results suggest that p300 can augment the activation of IL-18 by c-Fos. All these data implicate important roles of p300 in the transcriptional regulation of IL-18.

MATERIALS AND METHODS

DNA Constructs

A 1,490-bp fragment of IL-18 p1 promoter amplified by PCR from the mouse genomic DNA was cloned into the luciferase reporter construct pGL3 at *Xho*I site. Vectors of wild type p300 and mutated p300 with HAT deleted (mutp300) were provided by Cheong-Hee Chang (University of Michigan Medical School, Ann Arbor). Constructs of E1A 12Swt (wild type E1A) and E1A 12SΔ2–36 (mutated E1A that does not bind to p300/CBP) were gifts from Elizabeth Moran (Temple University School of Medicine, Philadelphia). The c-Fos expression vector was a gift from Richard M. Pope (Northwestern University Medical School, Chicago).

Cells and Transient Transfection

The J774 murine macrophage cells and 293T human embryonic kidney epithelial cells were maintained in DMEM supplemented with 10% FBS, 2 mM glutamine, 100 μg/ml of penicillin, and 100 μg/ml of streptomycin. Cells were activated by LPS (10 μg/ml) after transfection using a standard calcium phosphate method with 2.5×10^5 cells and 1 μg of DNA unless indicated otherwise.

RT-PCR of the Endogenous IL-18 mRNA

Total RNA was isolated from J774 cells (Promega Total RNA Isolation System). Mouse IL-18 cDNA was derived from 1 μg of total RNA by reverse transcription (RT) using Promega Reverse Transcription System. PCR was performed with specific primers, yielding a 360-bp product. The following primer sequences were used: 5′AAAGTGCCAGTGAACCC3′ and 5′TTTGATGTAAGTTAGTGAGAGTGA3′. RT-PCR products were amplified in the linear range. An equal aliquot of cDNA was amplified with β-actin primers. The specific β-actin PCR

product was 611 bp in size. Aliquots of PCR reactions were separated on a 1% agarose gel and visualized with UV light after ethidium bromide staining. The semi-quantitative estimation of the RT-PCR products was accomplished by photodensitometric analysis of the bands in agarose gel after electrophoresis, and the results were expressed as the relative ratio between intensity values of IL-18 and β-actin PCR bands.

Luciferase Reporter Gene Assays

293T cells were activated with LPS (10 μg/ml) (Sigma-Aldrich, St. Louis, MO) 16 h after transfection and were analyzed for luciferase activity 16 h after the treatment with LPS using a Promega Dual-Luciferase Reporter Assay System. As a transfection control for the luciferase assays, the Renilla luciferase control plasmid was cotransfected in all experiments. Transfections were normalized to Renilla luciferase as indicated in the figure legends. Relative luciferase activity (RLA) was calculated using the luciferase activity of cells transfected with the reporter DNA alone as 1 unless noted. All the results represent the mean ± standard deviation (SD)from at least three independent experiments. Microsoft Excel was used for both graphic drawing and data analysis.

RESULTS AND DISCUSSION

Transcription of IL-18 mRNA Was Increased by p300

LPS stimulates the secretion of IL-18 in wild type J774 cells. To know if p300 would enhance the LPS- stimulated IL-18 expression, J774 cells were transfected with the p300 expression vector and the amount of IL-18 mRNA was analyzed by RT-PCR. The RT-PCR products were resolved by agarose gel electrophoresis, quantified by photodensitometry, and expressed as a ratio between the readings of IL-18 gene and those of β-actin gene (a house-keeping gene used as internal reference). Figure 1A shows the RT-PCR products in agarose gels, representing the levels IL-18 transcript after the cells were transfected with p300 vector. The photodensitometry data of the bands in Figure 1A are shown in Figure 1B. It is clear from these data that p300 was able to increase the transcription of IL-18 gene at very significantly different levels ($P < 0.01$) compared with those of the cells transfected with pcDNA3.1 control vector. Thus, p300 was able to promote the endogenous expression of IL-18 in J774 cells.

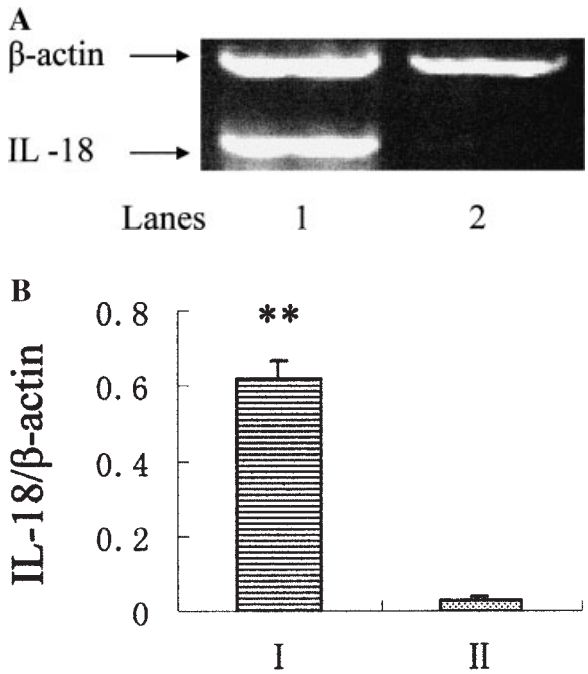

Fig. 1. IL-18 mRNA production in J774 cells was increased by p300. J774 cells was transfected with 3 μg p300 expression vector or pcDNA3.1 empty vector. RNA (1 μg) was reverse transcribed with an oligo(dT) primer, followed by PCR with either IL-18 primers or β-actin primers. Products were analyzed by agarose gel electrophoresis followed by ethidium bromide staining, and the photodensitometry analyzing. **A**: The IL-18 and β-actin products are indicated with arrows. **Lane 1**, mRNA level of the cells transfected with p300 expression vector; **lane 2**, mRNA level of the cells transfected with pcDNA3.1 empty vector. **B**: Results of photodensitometric analysis of RT-PCR products. I, The relative ratio between intensity values of IL-18 and β-actin PCR bands in (A), Lane 1; II, The relative ratio between intensity values of IL-18 and β-actin PCR bands in (A), lane 2. **, Very significant ($P < 0.01$).

p300 Activated the IL-18 Promoter in a Dose-Dependent Manner

Cotransfection studies were performed to assess the role of p300 on the IL-18 p1 promoter. We first examined whether p300 can activate the IL-18 promoter. 293T cells were transfected with the 1,490-bp IL-18 promoter-driven luciferase, and the p300 expression vector or the empty control vector. As a reporter, we used the region of the mouse IL-18 promoter containing 1,490 bp upstream of the transcriptional start site fused to the luciferase gene. This region is sufficient for the maximal transcriptional induction of the *IL-18* gene in response to multiple

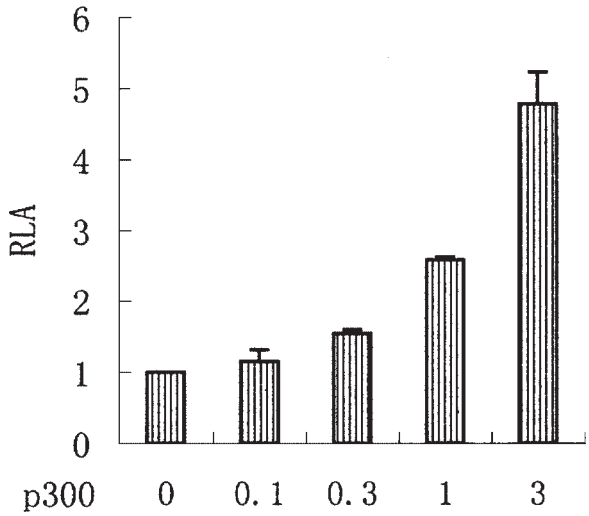

Fig. 2. Dose-response effect of p300 on the IL-18 promoter. 293T cells were transfected with 1 μg of the 1,490-bp IL-18 promoter-driven luciferase reporter vector, and increasing amounts (in micrograms) of the p300 expression vector as indicated. The amount of plasmid DNA for each transfection was adjusted by adding pcDNA3.1 DNA. All the results represent the mean ± standard deviation (SD) from at least three independent experiments.

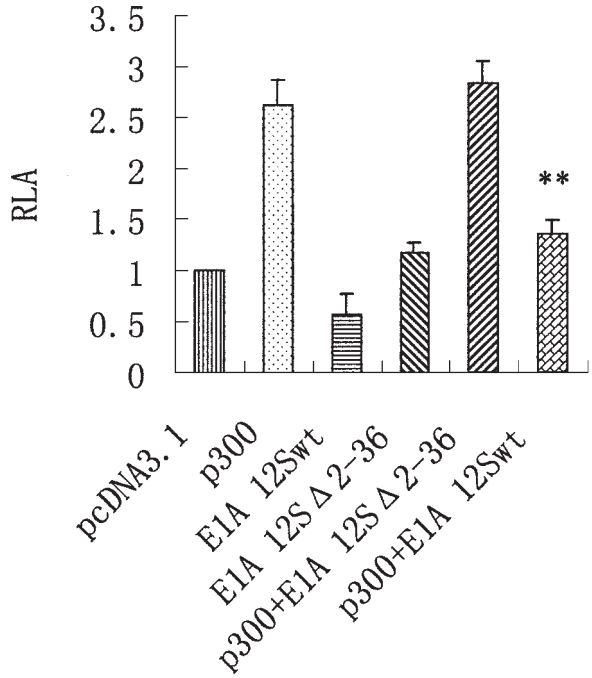

Fig. 3. Adenovirus E1A inhibited p300-mediated activation of the IL-18 promoter. E1A 12Swt or E1A 12SΔ2–36 was transfected with the IL-18 promoter-driven luciferase reporter vector and p300 expression vector. One μg of each DNA was used. *, Significant ($P < 0.05$). All the results represent the mean ± SD from at least three independent experiments.

signaling pathways. Figure 2 shows that the luciferase activity was enhanced by p300 in a dose-dependent manner, further indicating that p300 is involved in the activation of the IL-18 promoter.

Adenovirus E1A Protein Inhibits p300-Mediated Activation of the IL-18 Promoter

Adenovirus E1A and the E1A-mimicking cellular transcription factor Twist bind the acetyltransferase region of p300 and inhibit its acetyltransferase activity [Wang et al., 1993; Chakravarti et al., 1999; Hamamori et al., 1999]. To confirm the functional effect of p300, we cotransfected cells with a vector expressing E1A 12Swt together with p300. As a control, we used a mutant form of the protein (E1A 12SΔ2–36), which lacks the p300/CBP interaction domain and fails to inhibit p300/CBP activity [Wang et al., 1993]. The results showed that the wild type E1A12S, but not the mutant E1A without the p300-binding domain, abolished p300-mediated activation of the IL-18 promoter (Fig. 3). As can be seen in Figure 3, activation of the IL-18 reporter gene upon stimulation of 293T cells with LPS was strongly inhibited by E1A 12Swt but not by E1A 12SΔ2–36. When cotransfected with E1A 12Swt, the activity of the IL-18 p1 promoter reporter was significantly different from that cotransfected with E1A 12SΔ2–36. This experiment provided further evidence that p300 is functionally involved in IL-18 promoter activation.

The Acetylase Activity of p300 Was Necessary for Activating IL-18 Promoter

p300 first stepped into the limelight as a protein associated with the adenovirus E1A oncoprotein as early as in 1989 [Whyte et al., 1989], but it is not endowed with HAT activity until 1996 [Ogryzko et al., 1996]. Since the discovery that p300 possesses acetyltransferase activity, many studies have been focused on the role of p300 as an acetyltransferase. In order to determine whether the HAT activity of p300 is necessary for its function in promoting IL-18 expression, we performed cotransfection studies with the p300 with HAT domain deleted (mutp300). As shown in Figure 4, wild type p300 enhanced IL-18 promoter activity while the mutp300 did not have this effect. The activities of IL-18 p1 promoter between the cells cotransfected with p300 and the cells cotransfected with mutp300 were very significantly different

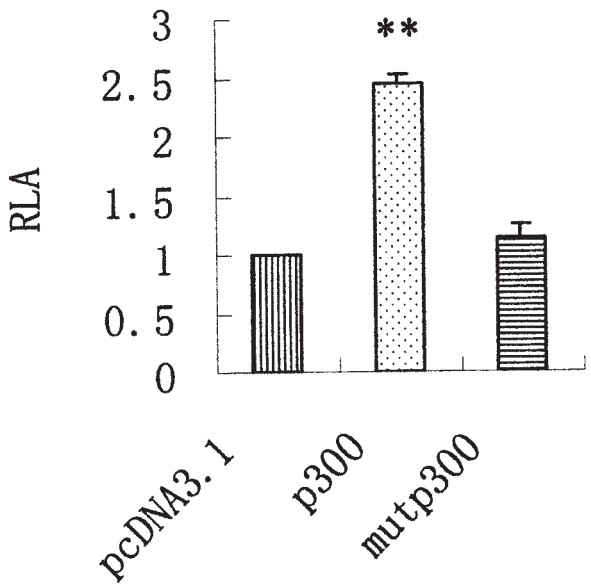

Fig. 4. The HAT activity of p300 was necessary for IL-18 activation. IL-18 promoter-driven luciferase vector was co-transfected with the wild type p300 or mutp300 vector. One μg of each DNA was used. **, Very significant ($P < 0.01$). All the results represent the mean ± SD from at least three independent experiments.

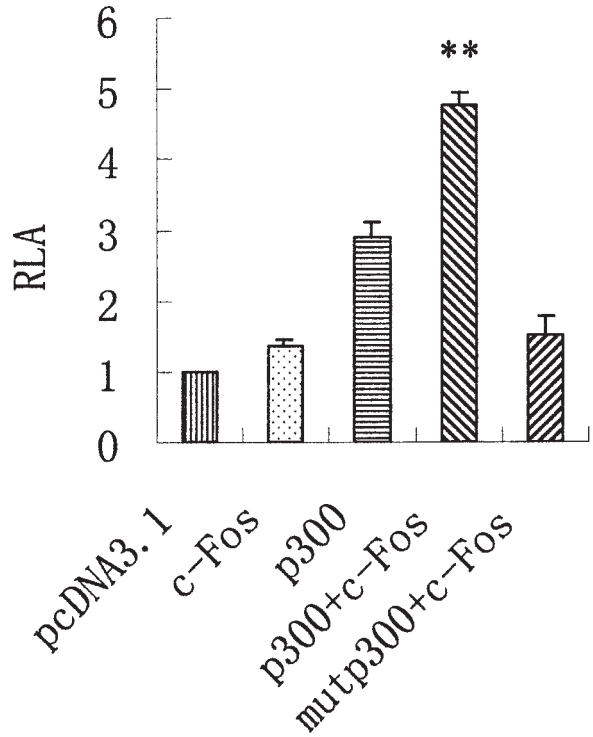

Fig. 5. p300 enhanced the c-Fos-mediated activation of the IL-18 promoter. Wild type p300 or mutp300 was transfected with the IL-18 promoter-driven luciferase vector and c-Fos expression vector. One μg of each DNA was used. **, Very significant ($P < 0.01$). All the results represent the mean ± SD from at least three independent experiments.

($P < 0.01$). This result suggested that the HAT activity of p300 was necessary for its action.

p300 and c-Fos Worked Synergistically to Enhance the Activation of IL-18 Reporter Gene

Many transcription factors recruit p300/CBP and P/CAF coactivators, which participate in the activation of target gene transcription [Fontes et al., 1999; Fax et al., 2000; Schuringa et al., 2001]. p300 and CBP have been reported to be able to directly acetylate transcription factors [Marzio et al., 2000; Kawai et al., 2001]. Among these transcription factors, AP-1 is an essential transcription factor regulating IL-18 gene transcription [Kim et al., 2000]. c-Jun and c-Fos are two subunits which constitute the biologically active AP-1. There is evidence to show that either of these two subunits can bind to and transactivate many genes in vitro [Lee et al., 1996; Albanese et al., 1999; Brockmann et al., 1999; Preston et al., 2000]. In order to understand whether p300 plays a role in the activation of IL-18 by AP-1, we investigated the effect of p300 on c-Fos. As shown in Figure 5, wild type p300, but not the mutp300, worked synergistically with c-Fos to enhance the activation of IL-18 reporter gene. The RLA of cells transfected with p300 was very significantly ($P < 0.01$) different from that of cells transfected with mutp300. The coactivator p300 acts as a transcriptional adaptor for many DNA-binding activators. The findings that p300 possesses intrinsic acetyltransferase activity has greatly advanced our understanding of its function [Ogryzko et al., 1996]. On the other hand, the acetylase activity of p300 was not always necessary for its action on transcription factors. For example, when it activated the Sp1, its function was acetylation-independent [Suzuki et al., 2000]. Our results suggested that p300 can enhance the activation of IL-18 promoter mediated by c-Fos, and the HAT activity of p300 is necessary for this synergistic action.

To summarize, based on all these results from the co-transfection experiments, we have reached the conclusion that p300 can increase the endogenous IL-18 mRNA and acts as an acetyltransferase on the exogenous IL-18 promoter. Further studies will be performed to define the molecular basis for p300-mediated enhancement of LPS activation of IL-18.

ACKNOWLEDGMENTS

We thank Cheong-Hee Chang, Elizabeth Moran, Richard M. Pope for providing plasmid constructs.

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