Signal transducers and activators of transcription (Stat) belong to a family of latent cytoplasmic factors that can be activated by tyrosine phosphorylation by members of the JAK tyrosine kinase family in response to a variety of cytokines and growth factors. Activated Stats form dimers and translocate into nucleus to induce expression of critical genes essential for normal cellular events. Here we report for the first time that Stat3 can be modified by acetylation both in vivo and in vitro. A major site of Stat3 that is acetylated by its coactivator, p300/CREB-binding protein (CBP), resides in the C-terminal transcriptional activation domain at lysine 685. Furthermore, the acetylation of Stat3 can stimulate its sequence-specific DNA binding ability and transactivation activity. Inhibition of histone deacetylase activity in cells results in increased Stat3 nuclear localization. These observations clearly indicate a novel mechanism for Stat3 activation in mammalian cells.

Signal transducer and activator of transcription 3 (Stat3) protein is a latent cytoplasmic transcription factor involved in cytokine, hormone, and growth factor signal transduction. It plays a key regulatory role in various cytokine-controlled cellular processes such as acute phase and immune responses, differentiation, proliferation, and cell survival (1, 2). Upon stimulation, Stat3 can be activated by tyrosine phosphorylation at a single site close to the C terminus (Tyr-709). This phosphorylation is required for Stat3 dimerization, nuclear translocation, and DNA binding (3). Stat3 has been implicated in cancer processes (4, 5). In fact, constitutive activation of Stat3 has been detected in many cancer cells and tissues as well as in a variety of experimental malignancies, including those of multiple myeloma, leukemia, lymphoma, breast, ovarian, lung, prostate, and gastric cancers (4–9). In these malignancies, Stat3 has been described as mediating largely a survival function by activating antiapoptotic genes such as Bcl-2 and Bcl-X (4, 10).

It is widely accepted that Stat3 is activated by tyrosine kinases, mostly the Jak1 kinase upon stimulation. Activated Stat3 then dimerizes and translocates into the nucleus, where it binds specific promoter sequences of target genes and induces transcription (1–3). The dimerization is through the interaction between the SH2 domain of one Stat3 and the tyrosine-phosphorylated tail segment of the other Stat3. Both the ability to translocate into the nucleus and the ability to bind DNA are attributed to this dimerization. Although numerous studies support this model (reviewed in Ref. 11), a number of recent studies have provided evidence suggesting that Stat3 exists as a dimer prior to its activation (11–14). Furthermore, studies on Dd-STATb, a Dictyostelium Stat protein with a highly aberrant SH2 domain, demonstrated that the activation of Dd-STATb did not rely on orthodox SH2 domain:phosphotyrosine interaction (15). These studies suggested that other types of activation mechanisms may exist.

Histone acetyltransferase CBP/p300 are important transcriptional coactivators capable of regulating many cellular processes. They can interact with a wide range of DNA binding transcription factors, including p53, E2F, AP-1, MyoD, and NF-κB (16). Specifically, CBP/p300 has been reported to interact with Stat proteins and regulate their function (16–23). The C-terminal transactivation domain of Stat3 interacts with CBP/p300 and activates transcription of its target genes (16, 21, 23). Here, we report that CBP/p300 can directly acetylate Stat3 protein in its C terminus both in vitro and in vivo. Acetylation of Stat3 increases its DNA binding ability and transactivation activity. Interestingly, cells treated with histone deacetylase inhibitors display an increase of Stat3 in the nucleus. Our data suggest that acetylation may provide an alternative mechanism for Stat3 activation.

**EXPERIMENTAL PROCEDURES**

**Culture Medium and Reagents—**HEK293 and HepG2 cells were cultured in Dulbecco’s modified Eagle’s medium supplemented with 10% fetal bovine serum. Human IL-6, TSA, and nicotinamide were purchased from Sigma. Anti-Stat3 (F-2, C-20) antibodies were purchased from Santa Cruz Biotechnology (Santa Cruz, CA). Anti-acetylated-lysine antibody was purchased from Cell Signaling Technology (Beverly, MA).

Detecting Stat3 Acetylation in Cells—In a transiently transfected Stat3 acetylation assay, HEK293 cells were transfected by calcium phosphate method with 10 μg of FLAG-Stat3 plasmid DNA. 10 ng of CMV-p300, or 10 μg of CMV-FLAG p300 DNA. 36 h after transfection, cells were lysed in a FLG lysis buffer (50 mM Tris, 137 mM NaCl, 1 mM NaF, 1 mM NaVO₄, 1% Triton X-100, and 0.2% sarkosyl, 1 mM dithiothreitol, 10% glycerol, pH 7.8) containing fresh protease inhibitors, 10 μM TSA, and 5 mM nicotinamide. Cell extracts were immunoprecipitated with anti-FLAG monoclonal antibody M2 beads (Sigma). After elution with the FLAG peptide, the proteins were resolved by either 8 or 4–20% SDS-PAGE gels (Invitrogen) and analyzed by Western blot with anti-acetylated lysine or anti-Stat3 antibodies. For endogenous Stat3 acetylation assay, HepG2 cells were treated with 5 ng/ml IL-6 alone or...
treated with 1 μM TSA and 5 mM nicotinamide for 6 h before harvest. Cell pellets were lysed in radioimmune precipitation buffer (10 mM Tris-HCl, pH 7.4, 150 mM NaCl, 1% Nonidet P-40, 1% deoxycholic acid, 0.025% SDS, and 1 mM phenylmethylsulfonyl fluoride) with mild sonication. The cell extracts were immunoprecipitated with anti-Stat3 (C-20) antibody and protein A/G beads (Santa Cruz Biotechnology). The beads were washed with 0.5 ml of radioimmune precipitation buffer five times and eluted by SDS sample buffer. The samples were further analyzed by Western blot with anti-acetylated lysine or anti-Stat3 (F-2) antibodies.

**In Vitro Acetylation Assay—GST-Stat3NT, M, CT constructs were a gift from Dr. J. Jung (Harvard Medical School). GST-Stat3CT1, CT2, CT3, CT3–1, CT3–2 constructs were made by inserting the PCR fragments into the plgEX2TL vector. All plasmids were transformed into Escherichia coli BL21 competent cells. The proteins were induced by 0.1 mM isopropyl-1-thio-β-d-galactopyranoside at 25 °C overnight, extracted with buffer BC500 (20 mM Tris-HCl, pH 8.0, 500 mM NaCl, 0.5 mM EDTA, 20% glycerol, 1 mM dithiothreitol, and 0.5 mM phenylmethylsulfonyl fluoride) containing 1% Nonidet P-40, and purified by G50 Sephadex beads (Novagen). Acetylation assays were performed essentially as described (24) with some modifications. In the standard assay, 20-μl reactions contain 50 mM HEPES (pH 8.0), 10% glycerol, 1 mM dithiothreitol, 1 mM phenylmethylsulfonyl fluoride, 10 mM sodium butyrate, 1 μl of [3H]acyetyl-CoA (55 mCi/mmol, Amersham Biosciences), about 2.0 μg of GST fusion proteins, and 100 ng of p300-(1195–1810) were incubated at 30 °C for 2 h. The reaction mixtures were subjected to SDS-PAGE gels and autoradiography. Gels containing 3H-labeled proteins were fixed with 10% glacial acetic acid and 40% methanol for 30 min and were enhanced by a fluorography enhancing solution (Amplify, Amersham Biosciences) for 30 min. Gels were then dried, and autoradiography was performed at −70 °C for 1–3 days.

**Electrophoretic Mobility Shift Assay—** EMSA was carried out essentially as described (25) with some modifications. The probe (24 bp) was generated by annealing the single-stranded oligonucleotide 5’-gaccttgtgggactaggctag-3’ and its complementary sequence. The probe was 32P end-labeled using T4 polynucleotide kinase and purified by MicroSpin G-50 column (Amersham Biosciences). The DNA binding reactions (20 μl) contain 20 mM Tris-HCl (pH 7.5), 50 mM KCl, 5 mM MgCl2, 1 mM dithiothreitol, 0.5 mM EDTA, 10% glycerol, 0.5 mg/ml bovine serum albumin, and 100 ng of poly(dI-dC) and proteins as indicated. Reaction mixtures were preincubated at room temperature for 30 min before a 32P-labeled DNA probe was added and then further incubated at room temperature for 30 min. The mixtures were then resolved on a native 4% polyacrylamide gel at 4 °C followed by autoradiography.

**Dual Luciferase Assay—** HepG2 cells were seeded at 2 × 104 cells/well in 6-well plates and were transfected using the calcium phosphate precipitation method after 24 h, with pLucTK3 (26), pRL-TK, and different Stat3 and CBP plasmids as indicated. 36 h after transfection, cells were treated with 5 ng/ml IL-6 for 6 h and then lysed in 500 μl of passive lysis buffer and subjected to the dual luciferase assay according to the manufacturer’s menu (Promega). Experiments were performed in triplicate and at least five independent times.

**Immunofluorescence Assays—** Cells were seeded onto duplicated poly(Mowiol) (Polysciences), and the slides were examined under an Olympus IX71 microscope.

## RESULTS

### Stat3 Is Acetylated by CBP/p300 in Vivo—
To test whether Stat3 could be acetylated by CBP/p300, we first used a transient transfection assay. As indicated in Fig. 1A, a high level of acetylated Stat3 was found in the cells cotransfected with either Stat3 and p300 or Stat3 and CBP (lanes 2 and 3). However, there was no detectable acetylated Stat3 in overexpressed Stat3 alone in the transfected cells (lane 1). We further tested whether the endogenous Stat3 can be acetylated in vivo. HepG2 cells were used to immunoprecipitate endogenous Stat3 protein. In unstimulated HepG2 cells, no obvious acetylated Stat3 was detectable (Fig. 1B, lane 1). After stimulation of HepG2 cells with IL-6, the acetylation of Stat3 can be clearly detected (Fig. 1B, lanes 2–6). Stat3 acetylation can be detected as early as 20 min after stimulation (Fig. 1B, lane 2), indicating that acetylation is an early event in Stat3 signal transmitting upon stimulation. Our previous study on p53 acetylation showed that maximum induction of p53 acetylation requires inhibition of both category I (HDAC1) and category III (Sir2) histone deacetylase activity by treatment with TSA (for HDAC1) and nicotinamide (for Sir2 (28)). Here, we tested the ability of these drugs to increase the endogenous Stat3 acetylation level. As indicated in Fig. 1C, an increased level of acetylated Stat3 was evident when cells were treated with IL-6, TSA, and nicotinamide when compared with acetylation level from IL-6 treatment alone (lane 3 versus lane 2). Thus, these data indicate that Stat3 can be acetylated in vivo after stimulation. Furthermore, inhibition of histone deacetylase activity increases the level of Stat3 acetylation.

![Fig. 1. Stat3 is acetylated by CBP/p300 in vivo. A, acetylation assay in transiently transfected HEK293 cells. Upper and lower panel, Western blot analysis of the anti-FLAG M2 immunoprecipitated Stat3 with anti-acetylated lysine antibody (upper panel) and anti-Stat3 (C-20) antibody (lower panel). The transfection reactions were FLAG-Stat3 alone (lane 1), FLAG-Stat3 and CBP (lane 2), or FLAG-Stat3 and p300 (lane 3). B and C, endogenous Stat3 acetylation in stimulated HepG2 cells. Upper and lower panel, Western blot analysis of the immunoprecipitated Stat3 after 5 ng/ml IL-6 treatment for indicated time (B) or after IL-6, TSA, and nicotinamide (Nia) treatment (C) with anti-acetylated lysine antibody (upper panel) and anti-Stat3 (C-20) antibody (lower panel).](http://www.jbc.org/content/jbc/115/29/11529/F1.large.jpg)
Mapping Stat3 Acetylation Site—To map the p300-dependent acetylation site of the Stat3 protein, we used an in vitro acetylation assay. Stat3 GST fusion proteins were assayed for acetylation by p300 (described under “Experimental Procedures”) with reaction products analyzed by SDS-PAGE and autoradiography (upper panel) and GST fusion proteins analyzed by SDS-PAGE and Coomassie Blue staining (lower panel). The transfection reactions were FLAG-Stat3wt (lane 1), FLAG-Stat3K685R (lane 3), FLAG-Stat3K685Q (lane 5), FLAG-Stat3wt and CBP (lane 2), FLAG-Stat3K685R and CBP (lane 4), or FLAG-Stat3K685Q and CBP (lane 6).

**Fig. 2.** The Stat3 acetylation site is located at the C-terminal lysine 685. A, schematic representation of the Stat3 protein and different GST fusion proteins. B, in vitro acetylation assay. Stat3 GST fusion proteins were assayed for acetylation by p300 (described under “Experimental Procedures”) with reaction products analyzed by SDS-PAGE and autoradiography (upper panel) and GST fusion proteins analyzed by SDS-PAGE and Coomassie Blue staining (lower panel). C, acetylation assay for Stat3 K685R and K685Q proteins in HEK293 cells. Upper and lower panel, Western blot analysis of the anti-FLAG M2 beads immunoprecipitated Stat3 with anti-acetylated lysine antibody (upper panel) and anti-Stat3 (C-20) antibody (lower panel). The transfection reactions were FLAG-Stat3wt (lane 1), FLAG-Stat3K685R (lane 3), FLAG-Stat3K685Q (lane 5), FLAG-Stat3wt and CBP (lane 2), FLAG-Stat3K685R and CBP (lane 4), or FLAG-Stat3K685Q and CBP (lane 6).
endogenous Stat3 protein. Another possibility is that a weak acetylation site exists in another lysine residue. Nevertheless, we have mapped that the Stat3 major acetylation site by p300 is at the lysine 685.

**Stat3 Acetylation Augments Its Sequence-specific DNA Binding**—To examine the effect of acetylation on site-specific DNA binding, we tested the DNA binding activities of acetylated Stat3 on a 24-bp oligonucleotide probe containing consensus binding site for Stat3 (for the sequence, see “Experimental Procedures”). The unmodified Stat3 can bind to its sequence-specific DNA probe in an EMSA (Fig. 3A, lanes 2–4, and 3B), whereas significantly enhanced binding was observed with acetylated Stat3 (Fig. 3A, lanes 5–7, and 3B). This result indicates that acetylation of Stat3 is capable of enhancing its DNA binding activity. We further examined this DNA binding enhancement by acetylation with the constant amount of Stat3 proteins and the cold competitor oligonucleotide for competition assay. A different amount of cold competitor was preincubated with Stat3 proteins for 30 min before the labeled probe was added to the binding mixture for a 30-min incubation. As expected, the unacetylated Stat3 DNA binding activity was reduced to 58% in 20× cold probe and to 34% in 100× cold probe competition assay (Fig. 3C, lanes 2–4, and 3D). In contrast, acetylated Stat3 DNA binding activity was more dramatically reduced in the same assay, with 45% remaining in 20× cold probe and 5% remaining in 100× cold probe assay (Fig. 3C, lanes 2–4, and 3D).
Acetylation of Stat3 Increases Its Transcription Activity—To test the effect of acetylation on Stat3 transcriptional activity, we cotransfected HepG2 cells with the Stat3 and CBP expression vectors, along with a reporter construct pLucTKS3, which contains seven copies of a Stat3-specific binding site (26). After IL-6 treatment, CBP strongly enhanced Stat3 transactivation activity (Fig. 4A). This enhancement could be the effects of both Stat3 acetylation and histone acetylation. To further investigate the role of acetylation on Stat3 transactivation, the Stat3 acetylation mutants described above were used in the same reporter assay. The Stat3K685Q mutant that mimics the acetylated Stat3 strongly enhanced its transactivation activity when comparing with the Stat3K685R mutant that mimics the unacetylated Stat3 (Fig. 4B). These results demonstrated that the acetylation on Stat3 indeed can activate its transactivation activity.

Acetylation of Stat3 Increases Its Nuclear Localization—To further explore the physiological consequence of Stat3 acetylation, we examined the effect of acetylation on Stat3 cellular localization. The Stat3 protein is predominately located in the cytoplasm in unstimulated cells. It can be activated at cytokine receptors by tyrosine phosphorylation and rapidly translocated into the nucleus (1–3). HepG2 cells were used for immunostaining to examine the effect of acetylation on Stat3 cellular localization. As reported previously (31), the Stat3 protein was mainly localized in the cytoplasm of unstimulated cells (Fig. 5a). However, after IL-6 stimulation, the Stat3 protein accumulated in the nucleus (Fig. 5b). The Stat3 nuclear localization level was also increased when we treated unstimulated cells with histone deacetylase inhibitors TSA and nicotinamide (Fig. 5c). Furthermore, when stimulated cells were treated with histone deacetylase inhibitors, which enhance the Stat3 acetylation level in the cell (Fig. 1C, lane 3), we observed a significant increase of Stat3 in the nucleus (Fig. 5d). We found that 60.5% of cells treated with IL-6 alone showed an accumulation of Stat3 in the nucleus. Moreover, 85.5% of cells treated with both IL-6 and histone deacetylase inhibitors displayed an accumulation of Stat3 in the nucleus (Fig. 5e). These observations suggest that acetylation of Stat3 can increase Stat3 nuclear localization in line with its increased DNA binding activity.

**DISCUSSION**

CBP/p300 is a transcriptional coactivator that regulates Stat3 activity in vivo (16–23). The precise mechanism of this regulation remains unclear. We show here 1) that Stat3 is acetylated by p300 both in vitro and in vivo, 2) that the major Stat3 acetylation site is located at its C-terminal position lysine 685, 3) that acetylation on Stat3 enhances its DNA binding activity and transactivation activity, and 4) that in vivo acetylation of Stat3 protein increases its nuclear localization. These results suggest a possible alternative mechanism for transducing intracellular signals within the Jak-Stat pathway or at least to complement its tyrosine phosphorylation pathway. Previous studies on Stat6 acetylation have shown that IL-4 induces Stat6 acetylation in addition to phosphorylation, and both reactions are required for translational activation of the 15-LOX-1 gene (32). Conceivably, acetylation on Stat3 plays a critical role after Stat3 is phosphorylated and translocated into the nucleus, where the CBP/p300 located. Acetylated Stat3 strongly binds to DNA and may prevent the nuclear export of Stat3 and increase its transcriptional activation. Additionally, acetylated Stat3 may recruit the CBP/p300 acetyltransferase to the promoter of its target DNA, resulting in acetylation of the core histone. This recruitment plus chromatin modification may further activate expression of its target genes.

Unlike p53, which has multiple acetylation sites on its C-terminal lysine residues, we found that Stat3 protein is acetylated by CBP/p300 at a major site of lysine 685. This makes...
Stat3 acetylation difficult to detect both in vitro and in vivo. In fact, the in vitro acetylation assay shows that the Stat3 acetylation level is much weaker than the p53 acetylation level (Fig. 2B, lanes 3, 6, and 7 versus lane 9) in the same assay. Nevertheless, it seems that the single lysine acetylation is sufficient for its functional regulation, especially to increase its target DNA binding and transactivation activity. The investigation for more functional consequence on the Stat3 acetylation is underway. Several recent studies have showed that Stat3 forms a dimer without tyrosine phosphorylation (11–14). In addition, the acetylation site lysine 685 located between SH2 domain and transactivation domain (TAD, 2) suggests that it is possible that acetylation may regulate the formation of a Stat3 dimer. Furthermore, Stat3 is phosphorylated at tyrosine 705. Both acetylation and phosphorylation may act in synergy to regulate Stat3 activity. In fact, the study on Stat6 acetylation found that inhibition of Stat6 tyrosine phosphorylation by genistein reduced Stat6 acetylation levels in A549 cells (32). Further studies on the regulation of Stat3 activity by acetylation and phosphorylation cross-talk are underway.

Careful regulation of Stat3 subcellular distribution makes it ideal for rapidly transducing signals from the receptor to its targets. Stat3 predominately resides in cytoplasm of unstimulated cells; upon stimulation, it quickly translocates into the nucleus and binds to the DNA of target genes, inducing their expression. The nuclear export of Stat3 protein ensures that the signal transmitted by Stat3 is transient. A few hours after stimulation, most of Stat3 protein has been exported into cytoplasm (31). This export prepares Stat3 protein for the next round of signal transmitting. The finding of Stat3 protein maintaining a basal level in the nucleus and Stat3 protein shuttles continuously between the cytoplasm and the nucleus in unstimulated cells (31, 33) (Fig. 5a) indicates the dynamic regulation of Stat3 nuclear import and export. A fungal toxin leptomycin B blocks Stat3 nuclear export and results in the accumulation of Stat3 protein in the nucleus of unstimulated cells (31). Our data show that treating cells with histone deacetylase inhibitors to increase Stat3 acetylation levels (Fig. 1C, lane 3) results in increased Stat3 protein in the nucleus (Fig. 5, c and d). This suggests that acetylation of Stat3 may block Stat3 export into the cytoplasm. Therefore, the deacetylation of Stat3 is necessary for its export from the nucleus to the cytoplasm.

Similar to regulation on Stat3 signal transduction by tyrosine phosphorylation and dephosphorylation, Stat3 acetylation is also regulated by cellular histone deacetylase and acetyltransferase activities. The acetylation level of Stat3 protein is likely the balance of activity of acetyltransferase CBP/p300 and histone deacetylases. Studies on p53 acetylation found that p53 can be deacetylated by both PID/MTA2/HDAC1 (34) and mammalian Sir2 (28). Similar to p53, inhibition of these deacetylase activities in cells indeed increased the level of Stat3 acetylation.

**Fig. 5. Acetylation of Stat3 increases its nuclear localization.** a–d, immunofluorescence staining of HepG2 cells with anti-Stat3 (C-20) antibody after cells were treated with control (a), 5 ng/ml IL-6 (b), 1 nM TSA and 5 mM nicotinamide (Nia) (c), and 1 nM TSA, 5 mM nicotinamide, and 5 ng/ml IL-6 (d). The cells were examined in an immunofluorescence microscope with a × 60 objective and are representative of more than 100 cells. DAPI, 4′,6-diamidino-2-phenylindole. e, the immunostained cells were quantitated with the percentage of Stat3 nuclear localized cells. The result was an average of three experiments.
(Fig. 1C, lane 3). Moreover, treating stimulated or unstimulated cells with TSA and nicotinamide showed an increase in the accumulation of Stat3 in the nucleus (Fig. 5, c and d). These data suggest that the balance of Stat3 nuclear import and export in these cells has been disrupted. Conceivably, the basal level of Stat3 proteins in the nucleus has been acetylated when histone deacetylases have been inhibited. This acetylation prevents the export of Stat3 into the cytoplasm and results in an accumulation of acetylated Stat3 in the nucleus.

The precise mechanism of acetylation of transcription factors to facilitate DNA binding activity remains unclear. In general, a conformational change occurs in the protein that exposes its DNA binding domain and facilitates binding to its target sequences. Our data show that acetylation on Stat3 increases its DNA binding activity (Fig. 3), transactivational activity (Fig. 4), and nuclear localization (Fig. 5). It is logical to infer that the increase of Stat3 transactivation activity by acetylation could be the result of the tight DNA binding and increased Stat3 nuclear localization. On the other hand, CBP/p300-mediated transcription activation by Stat3 may also involve nucleosomal histone acetylation at the promoter region, and the acetylated Stat3 may be involved in recruiting CBP/p300 to the target promoter for histone acetylation. Our results indicate that acetylation of Stat3 may contribute, at least in part, to activate Stat3 target genes in vivo by increasing its sequence-specific DNA binding activity and its nuclear localization. Although the steady state level of acetylated Stat3 is low in stimulated cells (Fig. 1C, lane 2), we found that Stat3 can be fully acetylated at the CBP/p300 site in stimulated cells when the cellular deacetylase activity is inhibited (Fig. 1C, lane 3). Thus, it is possible that acetylation of Stat3 plays a critical role in initiating and maintaining the binding of Stat3 to its target DNA sequences. In conclusion, acetylation of Stat3 may act through multiple mechanisms to affect DNA binding, dimerization, and nuclear export and to synergistically regulate transcriptional activation in vivo.

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