Tat-controlled Protein Acetylation*

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Human immunodeficiency virus, type 1-encoded transactivator protein Tat is known to be a substrate of and to interact with several nuclear histone acetyltransferases (HATs). Here we show that Tat is a general inhibitor of histone acetylation by cellular HATs and that for at least one of them, CREB-binding protein (CBP), it induces a substrate selectivity. Indeed, in the presence of Tat, the acetylation of histones by CBP was severely inhibited, while that of p53 and MyoD remained unaffected. The C-terminal domain of Tat, dispensable for the activation of viral transcription, was found to be necessary and sufficient to interfere with histone acetylation. These results demonstrate that Tat is able to selectively modulate cellular protein acetylation by nuclear HATs and therefore to take over this specific signaling system in cells.

Recent investigations have shown that HIV-1-encoded transactivator protein Tat targets at least five different nuclear histone acetyltransferases (HATs) (1–5). Depending on the nature of the HAT involved, this interaction may have different functional consequences. In the case of Tip60 and TAF1, Tat seems to inhibit their HAT activity and consequently modulate the expression of cellular genes (5, 6). When it interacts with P/CAF, p300/CBP and GCN5, an increase in the transactivator potential of Tat on the HIV-1 LTR has been observed. In this latter case, it has also been shown that Tat is itself a substrate for these HATs (2, 7–9). Indeed, GCN5 and p300/CBP can acetylate Tat on its lysines 50 (Lys50) and 51 (Lys51) while P/CAF acetylates the viral protein on its lysine 28 (Lys28). The acetylation of these specific lysines on Tat seems to create a signal, which helps Tat in its diverse activities. The acetylation of Lys28 of Tat by P/CAF enhances its interaction with the positive transcription elongation factor complex b (8). The Tat-mediated recruitment of positive transcription elongation factor complex b and its interaction with the transactivation-responsive region (TAR) RNA enhance the processivity of the TAR RNA polymerase II elongation complex leading to a considerable increase in viral RNA production (reviewed in (10)). The acetylation of Lys50 leads to the dissociation of Tat from TAR (reviewed in Ref. 11). Moreover, it has recently been shown that the acetylation of Lys50 of Tat creates a strong binding site for the P/CAF bromodomain (12, 13). In this case, the bromo-domain of P/CAF effectively competes with the TAR RNA and helps the removal of Tat from TAR. The acetylation of different lysines of Tat therefore appears to create a code reminiscent of the histone code (14, 15), finely regulating the activity of the protein. Although the functional significance of Tat acetylation is relatively well understood, the consequence of the interaction of Tat with different HATs on their activities remains obscure.

Here we investigated this issue and found that Tat is a general inhibitor of histone acetylation by the cellular HATs. We have also found that in at least one case, that of CBP, Tat controls the choice of its potential substrates. Our data show that Tat, while remaining a substrate for these HATs, inhibits the acetylation of histones but not that of other specific cellular factors. The C-terminal part of Tat was found to be responsible for the selective inhibition of the HAT activity of GCN5 and CBP. These data strongly suggest that Tat largely uses the cellular acetylation signaling system to enhance the viral gene expression and to modulate that of some cellular genes.

MATERIALS AND METHODS

Plasmid Constructs—Gal4-GCN5 fusion construct was prepared by cloning the coding sequence of GCN5 generated by PCR and digested by EcoRI and XhoI restriction enzymes in pcDNA-Gal4 digested by the same enzymes. Primers used were: 5′-GCGAATTCATGCTGGAGGAGGAGATCTATGG-3′ (‘prime’ primer) and 5′-GAGCCTCTAGACTACTTGTCAATGGAGCTTCC-3′ (‘3′ primer). GST-Tat M6 and M7 fusion constructs were prepared by cloning the coding sequence of Tat mutants in pGEX5X3 vector as follows. Tat mutants (M6 = 67–101 and M7 = 87–101) were produced by PCR using appropriate primers: 5′-GGGGATCCCAACCAGCTCTCTATCAGAACCC-3′/5′-GGGGATCCCATGAAATATATGCGTTCG-3′ (‘prime’ primer) and 5′-GGATCTATCGAAGGGCTTGCTCTC-3′ (‘3′ primer). PCR products were digested by BamHI (for ‘5′ end) and EcoRI restriction enzymes and cloned in pGEX5X3 vector digested by the same enzymes. Tat M6 and M7 constructs were prepared by cloning the coding sequence of Tat mutants in pcDNA vector as follows. Tat mutants (M6 = amino acids 67–101 and M7 = amino acids 87–101) were produced by PCR using the appropriate primers: 5′-GGGGATCCCAACCAGCTCTCTATCAGAACCC-3′/5′-GGGGATCCCATGAAATATATGCGTTCG-3′ (‘prime’ primer) and 5′-GGATCTATCGAAGGGCTTGCTCTC-3′ (‘3′ primer). PCR products were digested by HindIII (for ‘5′ end) and EcoRI and cloned in pcDNA digested by the same enzymes.

In Vitro Acetylation—HAT assays were performed as described previously (6) by incubating recombinant HATs with their substrate as mentioned in the legends of the figures, in a 40-μl reaction buffer (25 mM Tris-HCl, pH 8, 10% glycerol, 100 mM NaCl, 0.1 mM EDTA, 0.2 mM phenylmethylsulfonyl fluoride, 1 mM dithiothreitol, and 0.1 μCi of [3H]acetyl-CoA). Protein acetylation was analyzed by SDS-PAGE and autoradiography or by “filter binding method”: reactions were loaded on filter paper pieces, washed three times with 50 mM NaHCO3/Na2CO3,
RESULTS

**Tat Inhibits the HAT Activity of CBP and GCN5**—An *in vitro* HAT assay was set up using recombinant GCN5 and CBP. In the presence of GST or increasing amounts of GST-Tat, Tip60, whose HAT activity was previously shown to be inhibited by Tat (6), was used as a control. Fig. 1 shows that GST-Tat, but not GST, greatly reduced the HAT activity not only of Tip60 but also of GCN5 and CBP ( Autorad panels). These results suggested that Tat could be a general inhibitor of histone acetylation by nuclear HATs. These data also suggest that Tat may have a dramatic effect on general histone acetylation and prompted us to investigate the effect of Tat on histone acetylation *in vivo* and *in vitro*.

**General Inhibition of HAT Activity by Tat in Vivo and in Vitro**—To investigate whether Tat was capable of interfering with the general cellular HAT activity, a series of experiments was set up. Purified GST-Tat, capable of entering cells, was incubated overnight with Jurkat cells. Cells were then treated 6 h with TSA to inhibit histone deacetylases, and the level of histone acetylation was monitored in the total cell extracts using an anti-acetylated H4 antibody. Fig. 2A shows that in the presence of Tat, the level of *in vivo* TSA-induced histone acetylation was significantly lower than that observed in the control.
The inhibition of general HAT activity by Tat was also confirmed in vitro. HeLa nuclear extracts, competent for in vitro transcription and rich in HAT activity, were used to evaluate the ability of Tat to interfere with the general HAT activity present in the extract. The extracts were incubated with [14C]acetyl-CoA and purified histones in the presence of either recombinant GST-Tat or GST as a control. Fig. 2B shows that Tat interfered with the acetylation of histones by the nuclear HATs present in the extract. To show that this action of Tat was specific on the HATs and not on another unrelated enzymatic activity present in the extract, we tested the effect of Tat on global kinase activity by incubating the extract with [γ-32P]ATP and either GST or GST-Tat (Fig. 2C). Interestingly, Tat seemed to activate or repress the phosphorylation of a few proteins present in the extract but there was no global inhibition of the kinase activities on the nuclear proteins in the presence of Tat. These experiments support the notion that the repression of histone acetylation by Tat is due to a specific action of the viral protein on the nuclear HATs present in the extract. To rule out the possibility of artifacts, we designed two additional experiments. First, Tat is itself a substrate of several HATs including GCN5 and CBP. One could argue that Tat would compete with the histones for acetylation by the HATs and therefore inhibit histone acetylation. To exclude this possibility, we tested the HAT inhibitory effect of a Tat mutated on lysines 50 and 51, the target lysines of both GCN5 and CBP, and compared it with the inhibitory effect of a wild type protein. Fig. 2D shows that this mutant inhibits the HAT activity of GCN5 (left panel) as well as that present in HeLa nuclear extracts (right panel) as efficiently as the wild type Tat. This result suggests that Tat does not inhibit histone acetylation through a substrate-based competition mechanism. Another reason for the repression of HAT by Tat could be the histone masking effect of Tat. Indeed, a Tat-histone interaction might hinder the access of the enzyme to the histones. This is very unlikely, because in cells or in nuclear extracts, the nonspecific binding of hundreds of other nuclear proteins with Tat would greatly reduce this nonspecific binding of Tat to histones. Nevertheless, to completely exclude this artifact, the interaction of Tat with histones under our HAT assay conditions was investigated. Fig. 2E shows that histone retention is comparable between GST and GST-Tat and is also identical to the background level of interaction of histones with Sepharose beads alone (lane 1). This experiment rules out the involvement of histone binding by Tat in inhibiting nuclear HAT enzymatic activity.

**Tat Interferes with the HAT-dependent Transcriptional Activation in Vivo**—Considering these data, we also predicted that Tat should interfere with the HAT-dependent transcriptional activation in vivo. To test this hypothesis, we took advantage of the fact that the HAT activity of CBP and P/CAF is directly involved in the activation of transcription when these enzymes are targeted to a promoter (16). Vectors encoding parts of CBP, P/CAF, or GCN5, including their HAT domain, fused to the DNA-binding domain of Gal4 were co-transfected with a reporter plasmid containing five Gal4-binding sites cloned upstream of the thymidine kinase promoter controlling the expression of a luciferase gene (Fig. 3A). As expected, compared with the Gal4-DNA-binding domain alone, the transcription of the reporter gene was activated by the HAT domain of CBP (Fig. 3B, compare lanes 4 and 5) and to a lesser extent by that of P/CAF and GCN5 (compare lane 7 with lane 8 and lane 10 with lane 11). The co-expression of Tat significantly decreased this transcription activation. From these experiments we conclude that Tat is capable of inhibiting the activity of CBP, P/CAF, and GCN5 in vitro as well as in vivo.

**Tat Induces a Substrate Selectivity for CBP**—Since several HATs have been shown to acetylate substrates other than histones, we also monitored the effect of Tat on the protein acetyltransferase activity of these enzymes. CBP appeared as a good candidate because it specifically acetylates several transcription factors such as MyoD (17) and p53 (18) in addition to histones. Purified p53 and histones were used as substrates for bacterially expressed CBP in the presence of GST alone or GST-Tat. Fig. 4A shows that CBP can efficiently acetylate both histones and p53 (Fig. 4A, lanes 2 and 3). The addition of GST-Tat specifically inhibited the acetylation of histones while that of p53 remained unaffected (Fig. 4A, lanes 4 and 5). The ability of CBP to acetylate MyoD in the absence and presence of Tat was also tested. Here again, while Tat efficiently inhibited histone acetylation, it slightly affected the ability of CBP to acetylate MyoD (Fig. 4A, lane 7). A mixture of p53 and MyoD remained acetylated by CBP in the presence of Tat, while the acetylation of histones was dramatically reduced (Fig. 4A, lane 9). Finally, we have also shown that, while Tat inhibits histone
acetylation by CBP, it does not interfere with its own acetylation by this enzyme (Fig. 4B). These data suggest that in the presence of Tat, CBP is able to discriminate between its potential substrates.

The C-terminal Domain of Tat Is Necessary and Sufficient to Inhibit Histone Acetylation by GCN5 and CBP—To have a better insight into the mechanism involved in the Tat-dependent inhibition of histone acetylation by CBP and GCN5, in vitro tests were first used to map the regions of Tat mediating this inhibitory activity. A series of recombinant Tat deletion mutants were tested for their effect on the HAT activity of CBP and GCN5 in an in vitro assay (Fig. 5A). The results obtained with mutants M1 to M4, harboring progressive C-terminal deletions, showed that a deletion of the C-terminal 86–101 amino acids of Tat (M1 mutant) completely abolished the repression of GCN5 and CBP HAT activities by Tat (Fig. 5B). The C-terminal domain of Tat seems then involved in the inhibition of these HATs. However, we had shown previously that this domain was dispensable for the Tat-GCN5 interaction and that the amino acids 20–48 region of Tat was necessary and sufficient to interact with GCN5 (2). To characterize more precisely the respective role of the GCN5-interacting (aa 20–48) and the C-terminal (aa 67–101) domains of Tat in its interaction with GCN5 and in the inhibition of the GCN5 HAT activity, a series of recombinant GCN5 deletion mutants was used (Fig. 5C). The results obtained with mutants M5 to M7 showed that the C-terminal 51–101 region of GCN5 was essential for the interaction with Tat and its inhibition of the GCN5 HAT activity (Fig. 5D). In vitro HAT assays were performed with recombinant GCN5-HAT domain in the presence of GST or GST-Tat wild type (WT) or mutants M5, M6, and M7 as indicated. The acetylation of histones was analyzed by filter binding assay. The mean values of three experiments are represented.
of GST-Tat mutant proteins was produced. These mutants are: M5, containing aa 20–48 region of Tat (GCN5-interacting domain); M6, aa 67–101 (HAT inhibitory domain); and M7, aa 20–48 fused to 67–101 (Fig. 5A). A GST pull-down assay confirmed the interaction between Tat aa 20–48 (M5) and GCN5 (Fig. 5C). A construct containing the C terminus of Tat fused to the GCN5-interacting domain also interacted efficiently with GCN5 (Fig. 5C, M7). Interestingly, the C-terminal inhibitory domain of Tat did not show any stable interaction with GCN5 (Fig. 5C, M6). A quantitative HAT assay was performed using the GCN5 HAT domain and the GST-Tat mutants described above were tested for their inhibitory effects on histone acetylation by GCN5. Surprisingly, we found that the C-terminal domain of Tat was as efficient as the full-length protein in inhibiting GCN5 (Fig. 5D, compare M6 to WT) and that the fusion of the GCN5-binding domain of Tat to this inhibitory domain did not increase the inhibition of histone acetylation by GCN5 (Fig. 5D, M7 mutant). The GCN5 interaction domain of Tat alone could not inhibit histone acetylation by GCN5 (Fig. 5D, M5 mutant). Taken altogether, these results show that the C-terminal domain of Tat, which is not involved in a stable interaction with GCN5, is necessary and sufficient to repress the HAT activity of GCN5.

The Repression of Histone Acetylation by Tat Is Not Required for the Tat-dependent Activation of Transcription from HIV-1 5′ LTR—The in vivo Gal4 targeting test was also used to evaluate the role of the Tat C-terminal domain in interfering with the activities of CBP, P/CAF, and GCN5. Interestingly, in vivo a larger deletion of the C-terminal domain of Tat was necessary to relieve the repressive activity of Tat than in vitro. Indeed, while the full-length Tat and M1 mutant (aa 1–86) repressed the transcriptional activity of CBP, Tat M2 mutant (aa 1–60) was unable to interfere with the CBP activity (Fig. 6A, compare lane 5 with lanes 3 and 4). However, for P/CAF and GCN5, the in vivo results approached those obtained in vitro, since the M1 mutant of Tat was not as efficient as the full-length protein in repressing the activity of these enzymes (Fig. 6A, compare lanes 9 and 14 with lanes 8 and 13, respectively). We could also show that in these experiments both M1 and M2 mutants were as efficient as the wild type Tat in inducing HIV-1 LTR transcriptional activity (Fig. 6B). These data demonstrate that the two mutants are efficiently produced and, most importantly, that the capacity of Tat to repress histone acetylation by the nuclear HATs is not required for and does not interfere with the Tat-dependent activation from HIV-1 LTR.

**DISCUSSION**

The recent literature strongly suggests that HIV-1 encoded transactivator, Tat, largely uses the acetylation signaling system to optimally accomplish its various functions. The most studied aspect of this phenomenon is the gain of function by Tat on the HIV LTR, consecutive to its interaction with HATs or to its acetylation. However, Tat seems to also modulate the activity of the cellular HATs, which may in turn control many cellular events regulated by protein acetylation. The present study strengthens this hypothesis by showing the inhibitory effect of Tat on the histone acetyltransferase activity of three specific HATs: Tip60, CBP, and GCN5. Moreover, the general action of Tat on the cellular HATs was further confirmed by demonstrating that Tat could specifically inhibit the use of histones as substrates by these HATs in vitro as well as in vivo. Indeed, Tat is not a mere inhibitor of the catalytic activity of these cellular HATs but is capable of conferring them a substrate specificity. This phenomenon was clearly demonstrated in the case of CBP, which showed a selective inhibition of histone acetylation compared with the non-histone substrates, p53 and MyoD. These observations suggest that Tat may block the access of histones but not of other substrates to the catalytic site of CBP. This hypothesis predicts not only that the inhibitory action of Tat would be dependent on the structure of the substrate but also that Tat may induce a change in the conformation of the targeted enzyme. A modification of the conformation of CBP/p300 by the Tat had also been suggested, since the HAT had a better interaction with the basal transcription factors TBP and TFIIIB in the presence of Tat peptide 41–45 (7). Interestingly, this Tat-induced change of conformation may as well be involved in a better recognition of certain substrates by p300/CBP, since in the presence of Tat, the enzyme efficiently acetylates the p50 subunit of NF-kB (19). Our investigations show that the C-terminal domain of Tat is involved in the control of the enzymatic activity of the targeted HATs. The same domain has been shown to be involved in the inhibition of histone acetylation by TAF1250 (5). Interestingly, in this case also, the C-terminal inhibitory region of Tat interacted with a much lower affinity with TAF1250 than the aa 18–36 region of Tat (20).

Deng and colleagues (7) have recently reported that Tat had no effect on the acetylation of free histone H4 by p300/CBP. This apparent discrepancy with the results presented here can be explained by our demonstration of the specific involvement of the 15 C-terminal amino acids of Tat in the inhibition of
histone acetylation by CBP and GCN5. Indeed, in their studies these authors used a Tat lacking these critical 15 amino acids of Tat 101, which were shown here to be necessary for the inhibition. Interestingly, our data also show that the inhibition of the cellular HAT activity by Tat is not involved in the capacity of Tat to stimulate transcription from HIV-1 5′ LTR. Indeed, M2 Tat mutant lacking the C-terminal HAT-repressor domain is as efficient as the wild type Tat in inducing transcription from the HIV-1 LTR. This observation suggests that the Tat-dependent inhibition of cellular HAT aims at the modulation of cellular gene expression rather than directly controlling viral gene transcription.

The ability to induce a general inhibition of histone acetylation has also been reported for several specific viral proteins. Indeed, Kaposi’s Sarcoma-associated herpesvirus-encoded protein, v-IRF, directly interacts with p300 and suppresses its enzymatic activity on histones, leading to a hypoacetylation of histones H4 and H3 in vivo (21). p300 is also the target of Epstein-Barr virus-encoded protein EBNA3C. The interaction of the viral protein with p300 leads to the inhibition of p300 HAT activity and consequently to histone hypoacetylation also in vivo (22). A hypoacetylation of histone H4 is also induced by the bovine herpes virus-1 VP22 protein (23). However these studies have not investigated whether, like Tat, these viral proteins were capable of inducing a substrate selectivity.

The Tat-induced HAT substrate selectivity described here is not unique, since several papers have also reported that the adenovirus-encoded protein E1A is capable of directly modulating the catalytic activity of several HATs. For instance, in the cases of p300/CBP and P/CAF, E1A not only modulates histone acetylation (24–28) but also, like what was reported here for HIV-1 Tat, induces a substrate selectivity (27, 29). Indeed, interestingly, a concentration of E1A able to induce an in vitro acetylation of histones and MyoD by p300/CBP inhibits the acetylation of transcription factors TR/RXR, TFIIEβ, and TFIIIF/Rap74 (27). E1A also inhibits the p300-mediated acetylation of the transcriptional activators p53 (25, 29) and E2F (28), as well as that of the high mobility group proteins HMG I/Y and HMG 14 (28). Considering the data presented here, we postulate that many viruses could have developed the capacity to target the cellular HATs and take over the acetylation signaling in infected cells to successfully accomplish their life cycle.

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